

# **Guidelines for the diagnosis and treatment of Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia**

**Nordic MDS Group**

8th update, May 2017

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## **Introduction**

Myelodysplastic syndrome (MDS) is a group of clonal bone marrow disorders characterized by ineffective hematopoiesis resulting in cytopenias and an increased risk of developing acute myeloid leukemia (AML). Myelodysplastic-myeloproliferative neoplasms (MDS-MPN) share myelodysplastic and myeloproliferative features. The prognosis varies from mild chronic anemia to profound pancytopenia and rapid progression to AML. The Nordic MDS Group (NMDSG) has conducted clinical trials in MDS since 1985 and have published on-line guidelines at [www.nmds.org](http://www.nmds.org) since 2003.

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## **News in issue 8**

We have included the WHO 2016 classification, interpretation of NGS-data for MDS and CMML in diagnostic work-up and prognostic evaluation. The section on iron chelation is updated.

## 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 randomized trial.

**Table 1.**  
**Levels of evidence**

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized trials
Ib	Evidence obtained from at least one randomized 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

### **Grades of recommendation**

Grade	Evidence level	Recommendation
A	Ia, Ib	Required: At least one randomized 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 randomized 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 cytopenia defined using standard laboratory values for cytopenias (Hb <130 g/L [males], <120 g/L [females], ANC <1.8 × 10<sup>9</sup>/L, platelets <150 × 10<sup>9</sup>/L)<sup>1</sup>.

Immunophenotyping by Flow cytometry is an additional tool for the detection of aberrant antigen expression patterns or pathological blast populations at diagnosis and during follow-up.

Chromosomal aberrations are detected in approximately 50 % of newly diagnosed MDS<sup>2</sup> and karyotyping should be performed in all cases with suspected MDS<sup>3</sup>.

Detection of mutations with next-generation sequencing may provide important additional information. The diagnosis of MDS requires integration of all findings.

**Table 2. 2016 revision to the WHO classification of MDS**

Entity name	Number of dysplastic lineages	Number of cytopenias	Ring sideroblasts as percentage of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis
<b>MDS-SLD</b>	1	1-2	< 15% / < 5% <sup>b</sup>	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
<b>MDS-MLD</b>	2-3	1-3	< 15% / < 5% <sup>b</sup>	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
<b>MDS-RS</b>			≥ 15% / ≥ 5% <sup>b</sup>	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
<b>MDS-RS-SLD</b>	1	1-2			
<b>MDS-RS-MLD</b>	2-3	1-3			
<b>MDS with isolated del(5q)</b>	1-3	1-2	None or any	BM < 5%, PB < 1%, no Auer rods	del(5q) alone or with 1 additional abnormality, except loss of chromosome 7 or del(7q)
<b>MDS-EB</b>					
<b>MDS-EB-1</b>	0-3	1-3	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
<b>MDS-EB-2</b>				BM 10–19% or PB 5–19% or Auer rods	
<b>MDS-U</b>					
<b>with 1% blood blasts</b>	1-3	1-3	None or any	BM < 5%, PB = 1% <sup>e</sup> , no Auer rods	Any
<b>with SLD and pancytopenia</b>	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	Any
<b>based on defining cytogenetic abnormality</b>	0	1-3	< 15% <sup>d</sup>	BM < 5%, PB < 1%, no Auer rods	MDS-defining abnormality <sup>e</sup>

MDS-EB, MDS with excess blasts; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single-lineage dysplasia; MDS-SLD, MDS with single-lineage dysplasia; MDS-U, MDS, unclassifiable; SLD, single-lineage dysplasia.

<sup>a</sup> Cytopenias defined as hemoglobin concentration < 100 g/L, platelet count < 100 × 10<sup>9</sup> cells/L, and absolute neutrophil count < 1.8 × 10<sup>9</sup> cells/L. Rarely, MDS can present with mild anemia or thrombocytopenia above these levels; PB monocytes must be < 1 × 10<sup>9</sup> cells/L. <sup>b</sup> If SF3B1 mutation is present. <sup>c</sup> 1% PB blasts must be recorded on ≥ 2 separate occasions.

<sup>d</sup> Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD.

<sup>e</sup> Unbalanced: Loss of chromosome 7 or del(7q), del(5q), isochromosome 17q or t(17p), loss of chromosome 13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13). Balanced: t(11;16)(q23.3;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), inv(3)(q21.3q26.2)/t(3;3)(q21.3;q26.2), t(6;9)(p23;q34.1).

**Table 3. 2016 revision to WHO classification of myelodysplastic/myeloproliferative neoplasms**

Disease	Peripheral blood findings	Bone marrow findings
<b>Chronic myelomonocytic leukemia (CMML)</b>	Peripheral blood monocytosis $> 1 \times 10^9/l$ Not meeting WHO criteria for BCR/ABL1-positive chronic myeloid leukemia (CML), primary myelofibrosis (PMF), polycythemia vera (PV) or essential thrombocythemia (ET) <sup>1</sup> No rearrangement of <i>PDGFRA</i> , <i>PDGFRB</i> or <i>FGFR1</i> $< 20\%$ blasts <sup>2</sup> If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and an acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells <sup>3</sup> OR the monocytosis (as previously defined) has persisted for at least 3 months and all other causes of monocytosis have been excluded	Dysplasia in one or more myeloid lineage <sup>1</sup> $< 20\%$ blasts <sup>2</sup>
<b>Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML)</b>	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophils and their precursors $\geq 10\%$ of leukocytes No <i>BCR-ABL1</i> fusion gene No evidence of <i>PDGFRA</i> , <i>PDGFRB</i> or <i>FGFR1</i> rearrangement or <i>PCMI-JAK2</i> (should be specifically excluded in cases with eosinophilia) No or minimal basophilia Monocytes $< 10\%$ of leukocytes Not meeting WHO criteria for PMF, PV or ET <sup>4</sup>	Hypercellular BM with granulocytic proliferation and granulocytic dysplasia with or without dysplastic erythroid and megakaryocytic lineages $< 20\%$ blasts in PB and BM
<b>Juvenile myelomonocytic leukemia (JML)</b>	I. Clinical and hematologic features (all 4 features mandatory). Peripheral blood monocyte count $> 1 \times 10^9/L$ , blast percentage in peripheral blood and bone marrow $< 20\%$ , splenomegaly, absence of Philadelphia chromosome ( <i>BCR/ABL1</i> rearrangement). II. Genetic studies (1 finding sufficient). Somatic mutation in <i>PTPN11</i> or <i>KRAS</i> or <i>NRAS</i> (germline mutations (indicating Noonan syndrome) need to be excluded) clinical diagnosis of NF1 or <i>NF1</i> mutation, germline <i>CBL</i> mutation and loss of heterozygosity of CBL (occasional cases with heterozygous splice site mutations). III. For patients without genetic features, besides features listed under I, the following criteria must be fulfilled: Monosomy 7 or any other chromosomal abnormality, or at least 2 of the following criteria: Hemoglobin F increased for age, myeloid or erythroid precursors on peripheral blood smear, GM-CSF hypersensitivity in colony assay, hyper phosphorylation of STAT	$< 20\%$ blasts. Evidence of clonality
<b>Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)</b>	Anemia Persistent thrombocytosis $> 450 \times 10^9/L$ Presence of <i>SF3B1</i> mutation or, in the absence of <i>SF3B1</i> mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features <sup>6</sup> . No <i>BCR-ABL1</i> fusion gene, no rearrangement of <i>PDGFRA</i> , <i>PDGFRB</i> or <i>FGFR1</i> ; or <i>PCMI-JAK2</i> ; no <i>t(3;3)(q21;q26)</i> , <i>inv(3)(q21q26)</i> or <i>del(5q)</i> <sup>7</sup> No preceding MPN, MDS (except MDS-RS), or other type of MDS/MPN	$< 1\%$ blasts in PB and $< 5\%$ blasts in BM Dyserythropoiesis in the BM with ring sideroblasts $\geq 15\%$ of erythroid precursors <sup>5</sup> . Abnormal megakaryocytes as observed in PMF or ET
<b>Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)</b>	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 <i>BCR-ABL1</i> fusion gene or rearrangements of <i>PDGFRA</i> or <i>PDGFRB</i>	Mixed MDS and MPN features $< 20\%$ blasts

<sup>1</sup> Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, while the presence of MPN features in the bone marrow and/or of MPN-associated mutations (*JAK2*, *CALR* or *MPL*) tend to support MPN with monocytosis rather than CMML. <sup>2</sup> Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes. Promonocytes are monocytic precursors with abundant light grey or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely-distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count. <sup>3</sup> The presence of mutations in genes often associated with CMML (e.g. *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical context can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in sub clones. Therefore caution would have to be used in the interpretation of these genetic results. <sup>4</sup> Cases of myeloproliferative neoplasms (MPN), particularly those in accelerated phase and/or in post-polycythemic or post-essential thrombocythemic myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the bone marrow and/or MPN-associated mutations (in *JAK2*, *CALR* or *MPL*) tend to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of *SETBP1* and/or *ETNK1* mutations. The presence of a *CSF3R* mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of chronic neutrophilic leukemia or other myeloid neoplasm. <sup>5</sup> 15% ring sideroblasts required even if *SF3B1* mutation is detected. <sup>6</sup> A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of *SF3B1* mutation together with a mutation in *JAK2* V617F, *CALR* or *MPL* genes. <sup>7</sup> In a case which otherwise fulfills the diagnostic criteria for MDS with isolated *del(5q)*-No or minimal absolute basophilia; basophils usually  $< 2\%$  of leukocytes.

Next generation sequencing (NGS), mutations in > 40 myeloid genes have recently been detected in approximately 90 % of MDS patients<sup>4,5</sup>. The most frequently mutated genes are summarized in Table 12.

Mutational screening by NGS of genes commonly mutated in myeloid malignancies is emerging as an integral part of the diagnostic work-up and in prognosis evaluation. In younger individuals (< 50 years) the possibility of congenital or hereditary conditions must be considered, especially in the presence of a positive family history, concomitant physical abnormalities (nail dystrophy, facial abnormalities) or unexplained liver/pancreas/pulmonary affections. These conditions include Congenital Dyserythropoietic Anemias (CDA), Telomere-associated syndromes including Congenital Dyskeratosis, Hereditary Sideroblastic Anemia, Fanconi Anemia (FA), Congenital Neutropenias (Kostmann, Schwachman-Diamond), Diamond-Blackfan Anemia (DBA), familial platelet disorders including those with *RUNX1* mutation, and *GATA2*-mutations. The most well-known hereditary myeloid malignancy syndromes are summarized in Table 13.

### **Patient history and examination**

- Detailed family history at least 2 generations back, including cancer, bone marrow failure, liver/lung disorders or early deaths.
- Prior chemotherapy or irradiation, occupational exposure, alcohol-use, concomitant medication.
- Tendency for bleeding or infection.
- Complete physical examination including spleen size.

### **Blood tests**

- WBC, differential, hemoglobin, platelet count, red blood cell indices (MCV, MCHC) and reticulocyte count.
- Folic acid, cobalamin, (homocysteine and methyl malonic acid if in doubt).
- Ferritin, LDH, bilirubin, haptoglobin, DAT (Coombs test), ALAT, ASAT, alkaline phosphatase, albumin, uric acid, creatinine, S-erythropoietin, S-protein electrophoresis.
- Screening for HIV, hepatitis B and C.
- PCR for parvovirus B19 in hypoplastic MDS.
- If suspicion of telomere-associated disease, you may consider to contact regional coordinator for advice concerning analysis of telomere length and specific mutations.

### **Morphology**

Diagnostic work-up requires evaluation of bone marrow and peripheral blood smears for the assessment of dysplasia and blast counts together with histological examination of a bone marrow biopsy or clot, according to the WHO 2016 classification<sup>3</sup>. Repeated bone marrow examinations within a few weeks or months may be necessary to establish the diagnosis of MDS and to identify cases with rapid disease progression. In case of adverse genetics, severe pancytopenia or increased blast counts treatment should not be postponed by an additional bone marrow examination.

- Significant dysplasia within at least one lineage (erythro-, granulo-, or megakaryopoiesis), and is defined as  $\geq 10\%$  of cells with dysplastic features; a threshold of 30% is recommended for megakaryocytes.
- Blast count should be based on evaluation of at least 500 nucleated bone marrow cells (including erythroid) and 200 nucleated cells from peripheral blood.
- Marrow histology/immunohistochemistry: Evaluation of marrow sections provides additional information including cellularity, evidence of fibrosis, and marrow architecture including cell infiltrates or clustering. Immunohistochemistry for CD34 and p53 is recommended at

diagnosis and at follow-up. The presence of cells with strong nuclear p53 staining may indicate an underlying *TP53* mutation<sup>6</sup>.

**Cytogenetics**

- Standard karyotyping should be performed in all patients to allow correct classification and prognostic assessment.
- Next-generation sequencing (NGS): Mutational screening with NGS is recommended in potential transplant candidates of all MDS categories to further refine risk stratification and strengthen the diagnosis in borderline cases<sup>7,8</sup>.

**Clonal cytopenia of unknown significance (CCUS) and Idiopathic cytopenia of unknown significance (ICUS)**

Clonal hematopoiesis is gradually more prevalent in with increasing age and may be present in the absence of cytopenias (CCUS). The expanding clones typically harbor similar mutations observed in myeloid disorders and carries a variable risk of evolving to MDS. These patients should be monitored, and the number of mutations and variant allele frequency (VAF) are useful predictors of risk of progression (Table 4). Unexplained cytopenias without significant dysplasia or evidence of clonal hematopoiesis are classified as Idiopathic Cytopenia of Undetermined Significance (ICUS)<sup>9</sup>.

**Table 4. Comparison of genetic characteristic between CHIP, CCUS and MDS** (adapted from Bejar<sup>9</sup>)

	CHIP	CCUS at diagnosis	CCUS prior to MDS/AML progression	MDS all risk groups
Commonly mutated genes	<i>DNMT3A, TET2, ASXL1, PPM1D, JAK2, TP53</i>	<i>TET2, DNMT3A, ASXL1, SRSF2, TP53</i>	<i>TET2, SRSF2, ASXL1, U2AF1, DNMT3A</i>	<i>SF3B1, TET2, ASXL1, SRSF2, DNMT3A</i>
Mean number of mutations	~1	~1.6	~2	~2.6
Typical VAF	9-12%	30-40%	40 %	30-50%
Incidence	10-15% in 70-year olds	35% of ICUS	90% of ICUS	<50% of cytopenic patients
Risk of progression to MDS	0,5-1 % risk of transformation to a hematologic neoplasm <sup>10</sup>	Not applicable	Not applicable	Not applicable

Abbreviations: CHIP – clonal hematopoiesis of indeterminate potential, CCUS -clonal cytopenia of undetermined significance, ICUS – idiopathic cytopenia of unknown significant, VAF – variant allele frequency

**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. Differential diagnoses to be considered:

- B12 / folate deficiency
- Recent cytotoxic therapy
- HIV/HCV/HBV/Parvovirus B19/CMV/EBV-infection
- Anemia of chronic disease
- Autoimmune cytopenia

- Chronic liver disease
- Excessive alcohol intake
- Exposure to heavy metals
- Drug-induced cytopenias
- Other stem cell disorders incl. acute leukemia (with dysplasia or megakaryoblastic leukemia), aplastic anemia, myelofibrosis (in case of MDS with marrow fibrosis) and paroxysmal nocturnal hemoglobinuria (PNH)
- Other cancers infiltrating the bone marrow
- Congenital cytopenias/bone marrow failure disorders

## Prognosis

### IPSS for MDS (International Prognostic Scoring System)

(Greenberg et al, 1997<sup>11</sup>). The score excludes s/t-MDS and CMML with leukocyte count  $>12 \times 10^9/l$ . Online IPSS scoring: <http://nmds.hematology.dk/index.php/guidelines>

**Table 5. IPSS prognostic groups and score values**

**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	$\geq 2.5$	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	$\geq 2.5$	0.3	0.2

**Score values**

Prognostic variable	Score				
	0	0.5	1	1.5	2
BM blasts (%)	$<5$	5-10		11-20	21-30
Karyotype <sup>o</sup>	Good	Intermediate	Poor		
Cytopenias*	0/1	2/3			

<sup>o</sup> Good: normal, -Y, del(5q), del(20q). Poor: complex ( $\geq 3$  abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. \* Hemoglobin  $<100$  g/l, ANC  $<1.8 \times 10^9/l$ , platelets  $<100 \times 10^9/l$ .

## Revised IPSS (IPSS-R)

(Greenberg et al., 2012<sup>12</sup>). Based on 7012 untreated patients excluded s/t-MDS and CMML with leukocyte count  $>12 \times 10^9/l$ . Follow this link to perform online IPSS-R scoring:

<http://nmds.hematology.dk/index.php/guidelines>

**Table 6. IPSS-R prognostic groups and score values**

Prognostic subgroup (%)	Cytogenetic abnormalities	Median Survival (y)	Median AML evolution, 25%, y
Very good (4%)	-Y, del(11q)	5.4	NR
Good (72%)	Normal, del(5q), del(12p), del(20q), double incl. del(5q)	4.8	9.4
Intermediate (13%)	der(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor (4%)	-7, inv(3)/t(3q)/del(3q), double incl. -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very poor (7%)	Complex: > 3 abnormalities	0.7	0.7

Prognostic variable	Score						
	0	0.5	1	1.5	2	4	5
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blasts, %	$\leq 2\%$	-	$>2\% < 5\%$	-	5%-10%	$>10\%$	-
Hemoglobin	$\geq 100$	-	80- $<100$	$<80$			
Platelets	$\geq 100$	50- $<100$	$<50$				
ANC	$\geq 0.8$	$<0.8$					

Risk group	Risk score	Patients (%)	Survival (median, y)	AML transformation (25% of patients, y), 95% CI
Very low	$\leq 1.5$	19	8.8	NR (14.5-NR)
Low	$>1.5-3$	38	5.3	10.8 (9.2-NR)
Intermediate	$>3-4.5$	20	3.0	3.2 (2.8-4.4)
High	$>4.5-6$	13	1.6	1.4 (1.1-1.7)
Very high	$>6$	10	0.8	0.73 (0.7-0.9)

## Simplified risk categories (IPSS and IPSS-R)

In daily clinical practice, MDS is divided into "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. IPSS-R can be simplified into three risk groups, namely "low risk" including very low and low risk groups, "intermediate risk" and "high risk", the latter consisting of high and very high risk groups. Use of additional differentiating features could be of particular value for categorization of IPSS-R intermediate risk patients.

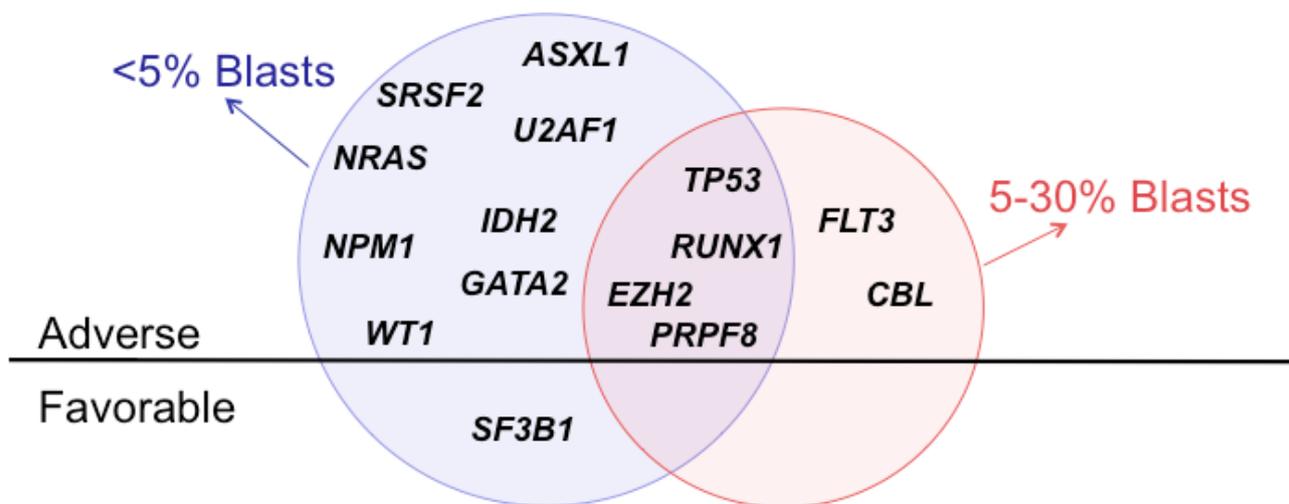
### Additional prognostic factors

- Comorbidity
  - MDS-specific comorbidity index (MDS-CI)<sup>13</sup> is based on: cardiac, liver, renal, pulmonary disease and solid tumors.
- Fibrosis
  - Bone marrow fibrosis grade 2 and 3 confers an inferior prognosis.

- Mutations associated with poor prognosis
  - *TP53*, *EZH2*, *ETV6*, *RUNX1*, *NRAS* and *ASXL1*<sup>8</sup>. Several mutated genes are linked to specific clinical risk factors.
- Mutations associated with higher bone marrow blasts and thrombocytopenia: *TP53*, *RUNX1*, *ASXL1*, *SRSF2* and *NRAS*,
- *TP53* mutation is associated with lower neutrophil counts and complex karyotype
- *SF3B1* mutation is associated with ring sideroblasts and a trend towards longer survival.

**Genes frequently mutated in MDS are listed in Table 12.**

- Mutations in *TP53*, *EZH2*, *RUNX1*, *ETV6*, and *ASXL1* associate with higher risk than predicted by IPSS and IPSS-R while mutations in genes such as *CBL*, *PRPF8*, *EZH2*, *PTPN11* and *NF1* have adverse prognostic associations independent of IPSS-R.
- Mutations in *ASXL1*, *SRSF2*, *U2AF1* and *SF3B1* have a prognostic significance thus only in patients with <5% blasts, while their prognostic significance is lost at higher blast counts (Figure 1)<sup>9</sup>. Additionally, the number of pathogenic variants in a patient has been found to be prognostically significant<sup>5,8,14,15</sup>.



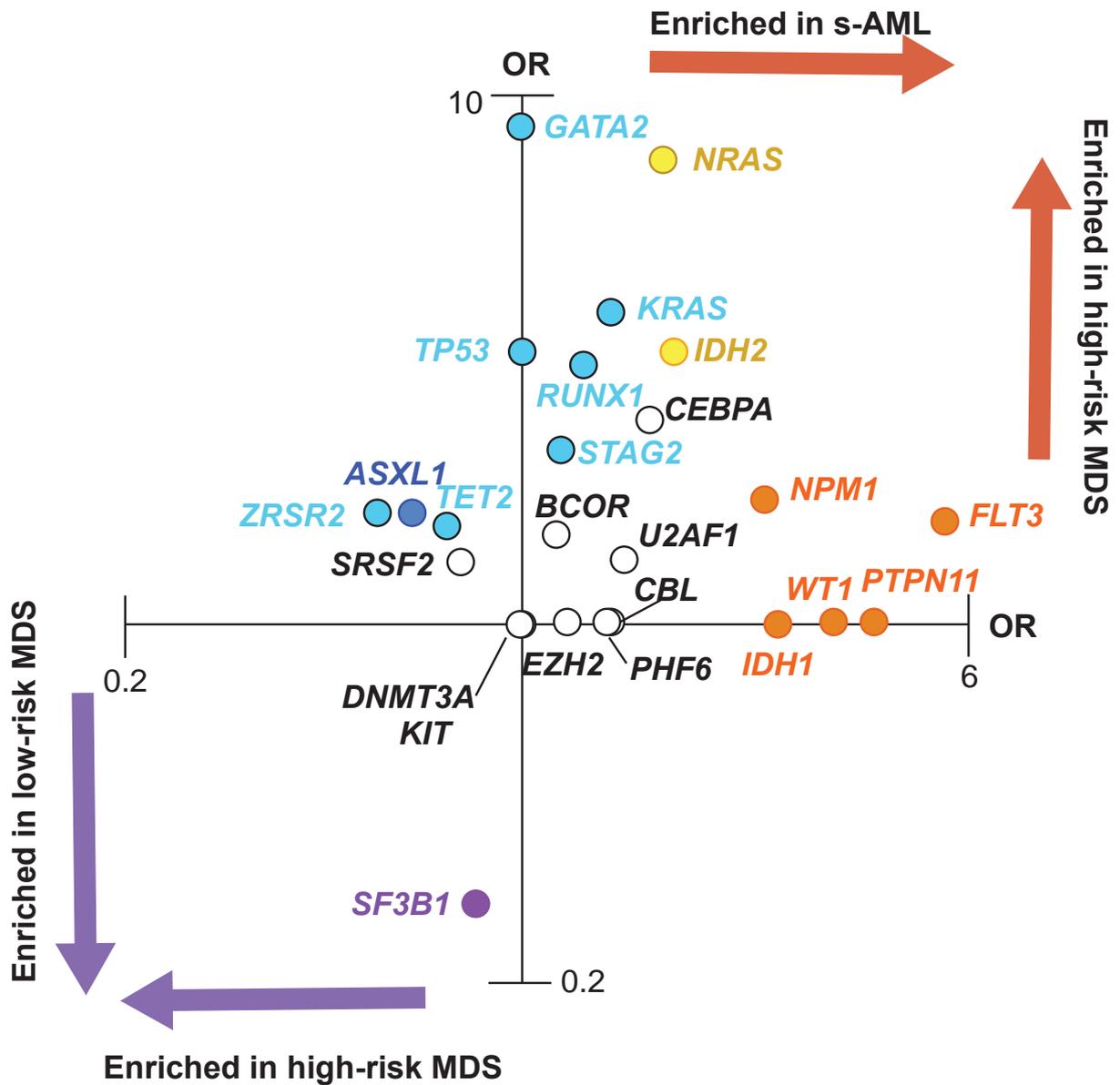
**Figure 1.** Mutated genes with independent prognostic significance by MDS bone marrow blast proportion. Genes in the figure are associated with overall survival after adjustment for IPSS-R risk groups. Genes in the blue circle are significant in patients with less than 5% blasts in the bone marrow. Genes in the red circle remain significant in patients with higher blast counts. *SF3B1* mutations are independently prognostically favorable (Figure adapted from Bejar<sup>9</sup>).

A lot of work remains to outline the clinical relevance of the mutational pattern of MDS. Mutational screening is at the moment not required as a part of the routine work up, but we recommend that it should be performed when the patient candidate for allogeneic stem cell transplantation and in borderline cases.

**Recommendation for diagnosis and prognosis**

- All patients should be classified according to WHO 2016 classification.
- All patients should be risk stratified according to IPSS and IPSS-R.
- Additional prognostic features, such as bone marrow fibrosis, co-morbidity and molecular genetics may also be useful, as well as p53 analysis by immunohistochemistry or sequencing.

- MDS should be reported to the National Cancer registries in all Nordic countries and to MDS specific registries, if applicable.



**Figure 2.** Enrichment of mutations in s-AML and high risk MDS versus high-risk and low-risk MDS respectively. Enrichment of mutations expressed as odds ratio (OR) of mutation rates in s-AML vs high risk MDS (x-axis) and in high risk MDS vs low risk MDS (y-axis). Non-significant OR are represented by black circles. Adapted from <sup>16</sup>.

## International Working Group (IWG) modified response criteria

The IWG criteria<sup>17</sup> define four 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.

**Table 7.**

### **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 $\leq 5\%$ myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hb $\geq 110$ g/L, Platelets $\geq 100 \times 10^9/L$ , Neutrophils $\geq 1.0 \times 10^9/L$ Blasts 0%.
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by $\geq 50\%$ over pre-treatment but still $> 5\%$ Cellularity and morphology not relevant
Marrow CR	BM $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ 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 $\geq 50\%$ from maximum remission/response levels in granulocytes or platelets Reduction in Hb concentration by $\geq 15$ 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	$\geq 50\%$ increase in blasts Any of the following: At least 50% decrement from maximum remission/ response in granulocytes or platelets Reduction of Hb by $\geq 20$ g/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**

Haematological improvement	Response criteria (response must last at least 8 weeks)
Erythroid response (pre-treatment $< 110$ g/L)	Hb increase by $\geq 15$ g/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 $\leq 90$ g/L pre-treatment will count in the RBC transfusion evaluation
Platelet response (pre-treatment $< 100 \times 10^9/L$ )	Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%
Neutrophil response (pre-treatment $< 1.0 \times 10^9/L$ )	At least 100% increase and an absolute increase $> 0.5 \times 10^9/L$
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 $\geq 15$ g/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 a candidate for therapeutic intervention at disease progression, regular bone marrow analysis is recommended. However, it should be pointed out that the primary WHO classification of MDS should not be changed on the basis of follow-up bone marrow examination but the changes should be interpreted as e.g. progression of transformation.

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. Consider potentially curative treatment (allogeneic stem cell transplantation) for patients with IPSS-R intermediate, in particular in the case of additional risk factors (high-risk genetic features, bone marrow fibrosis, transfusion need, mutated p53 etc.). Special attention should be given to patients categorized as intermediate risk according to IPSS-R, since few therapeutic studies have so far used this category as a criterion.
2. For patients with anemia, consider EPO  $\pm$  G-CSF to patients with predictive score 0 or 1 according to the predictive model.
3. High-quality transfusion- and chelation therapy, when indicated.
4. Evaluate patients with MDS with single lineage dysplasia (MDS-SLD) and MDS with multiple lineage dysplasia (MDS-MLD) for immunosuppressive treatment.
5. Lenalidomide treatment for patients with IPSS-R low and intermediate risk MDS with isolated del(5q), who have failed growth factor treatment or are not eligible for this treatment according to the predictive model, and who are not p53 positive by immunohistochemistry. Extreme precaution with lenalidomide treatment in younger patients who may be eligible for SCT.
6. Patients with severe cytopenia and/or transfusion dependency who have failed other relevant therapies should be considered for experimental treatment within a clinical trial.

### **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. Supportive care only or experimental treatment within a clinical trial.

## **Supportive Care**

### **Transfusion**

A recent study suggests that quality of life is improved with higher target Hb levels for transfusion<sup>18</sup>. 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 transfusions:** Please see thrombocytopenia section.

## Iron Chelation

### *Background*

There are currently three different iron chelators available, Desferrioxamine (DFO) to be given preferably by iv or sc infusion, and Deferasirox and Deferiprone, both given orally, the latter only available in some Nordic countries. A large prospective phase 2 trial has been conducted in which 341 patients with MDS were treated with deferasirox for one year<sup>19</sup>. 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. There are no studies proving the effect of iron chelation on long-term outcome in MDS. No randomized trials comparing the efficiency of the different iron chelators have been conducted in MDS. In practice, oral chelation is generally the 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 recommended in patients for whom long term transfusion therapy is likely, generally meaning patients with low and INT-1 IPSS-score (Very low and Low risk in IPSS-R). Start treatment when S-Ferritin > 1500 µg/l, or after approximately 25 units red cell transfusions.
- For transfusion-dependent patients that may be candidates for a future allogeneic transplantation it is crucial to avoid iron overload, and iron chelation should then be considered preventive and be initiated at an earlier stage.

**Monitoring iron chelation:**

- The target Ferritin level is <1000 µg/l.

## Parenteral chelators

### **Desferrioxamine (DFO) treatment**

- 40 mg/kg (20-50 mg) by subcutaneous infusion over 8-12 hours 5-7 days per week.
- Alternatively give DFO 5-10 g via portable infusion pump in a venous port over 5 days when the patient receives blood transfusion.
- Vitamin C 2-3 mg/kg/d could be started 4 weeks after the onset of DFO therapy to improve iron excretion. Caution, higher doses may be associated with cardiac arrhythmia.
- 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 or deferasirox in usual doses.

**Recommendation:**

Recommendation grade B, evidence level III.

**Oral chelators****Deferasirox treatment**

- NB: Film-coated tablets available from December 2016. The new tablets can be taken with water or a small meal, and no prior dissolving is needed. The tablets have 3 dosages; 90, 180 and 360 mg, equivalent to 125, 250 and 500 mg for the old tablets. The new start dose will be 7-14 mg/kg with a target dose of 14-28 mg/kg. Compared to the old, dispersible formulation, better tolerance with less gastrointestinal side effects has been reported for the new tablets<sup>20</sup>.
- S- creatinine, S-ALAT and S-ASAT should be measured weekly the first four weeks of treatment, and then monthly. In case of elevated s-creatinine > 2 ULN, deferasirox should be interrupted and then restarted at lower dose.

**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.

**Thrombocytopenia****Background**

Thrombocytopenia is present in 40-65 % and is the primary cause of death in 12 % of all MDS patients. Thrombocytopenia is also associated with RUNX1 and TP53 mutations, an increased risk of leukemic transformation and reduced overall survival. MDS patients often also present with functional platelet defects and increased platelet destruction.

Platelet transfusion is the most important supportive care for clinically significant thrombocytopenia and approximately 10 % of MDS patients are platelet transfusion dependent at diagnosis. Although platelet transfusions are an effective way to increase the platelet levels transiently and thus can be used for active bleedings or before dental or other invasive procedures, they are expensive, associated with several risks as febrile or allergic reactions, transfusion-related acute lung injury and transmission of viral or bacterial infections. Frequent platelet transfusions also lead to allo-immunization which eventually renders the patient refractory to transfusions unless derived from an HLA-matched donor.

Lenalidomide treatment in MDS with 5q deletion is often associated with the development or worsening of thrombocytopenia and is considered a good prognostic sign for a response to the treatment. Azacitidine treatment is frequently associated with a worsening of thrombocytopenia, especially during the first two courses but reversal of thrombocytopenia early in the treatment is considered a positive predictive factor for response.

### ***Decision-making and treatment***

- 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.
- Tranexamic acid 500-1000 mg times 3-4 daily orally (or intravenously if severe bleedings) can be used for patients that are thrombocytopenic and actively bleeding.

### **Recommendation:**

Recommendation grade C, evidence level IV.

Immunosuppressive treatment (ATG +/- cyclosporine A) can be used to treat low- and intermediate-1-risk thrombocytopenic patients if they are considered good candidates for this treatment also for other parameters.

### **Thrombopoietin (TPO) receptor agonists**

Thrombopoietin (TPO) receptor agonists romiplostim (Nplate) and eltrombopag (Revolade) are approved for the treatment of immunological thrombocytopenic purpura (ITP). They have also been tested in several clinical studies for thrombocytopenic MDS patients, both as monotherapy and in combination with myelosuppressive drugs, with the aim of less bleedings, less need for platelet transfusions and better overall outcome given the possibility to administer treatment in full doses without delays. A Cochrane review<sup>21</sup> did not find enough evidence for recommending neither romiplostim nor eltrombopag in MDS.

### **Treatment and prevention of infections**

Infections should be treated promptly and with follow up of outcome. Routine use of prophylactic antibiotic treatment cannot be recommended, but may be considered in patients with repeated infections, please see ATG-therapy section below. We recommend to consider antifungal prophylaxis (e.g. posaconazol) in patients with high risk MDS receiving induction chemotherapy, as well as acyclovir. Neutropenic patients should be informed to contact the caregiver in any case of fever above 38°C for more than 4 hours or any temperature above 38.5°C.

### **G-CSF treatment**

G-CSF injections can be considered as prophylaxis for severely neutropenic patients with recurring, serious infections or during infectious episodes. Published data are limited. It may be considered during azacitidine treatment. Long-acting G-CSF has not been evaluated in MDS and cannot be recommended.

## Treatment of low-risk MDS

### Treatment of anemia with erythropoiesis stimulating agents

#### **Background**

Treatment with EPO may improve hemoglobin levels and abrogate transfusion need in low-risk MDS. Addition of G-CSF has a synergistic effect on erythroid progenitor cells, and may induce responses in EPO refractory patients. EPO improves quality of life, and significantly prolongs time to transfusion requirement<sup>22</sup>. Retrospective studies indicate a survival benefit, with no impact on AML transformation. Darbepoetin (DAR) has longer half-life than EPO but a comparable efficacy.

#### **Indication for treatment**

- Low risk MDS (IPSS low or intermediate 1, IPSS-R very low, low or intermediate).
- Symptomatic anemia, individual assessment, rarely reasonable to start treatment if hemoglobin level >100 g/l
- Predictive score for response 0 or 1 point

**Table 8. Predictive score for response to erythropoiesis stimulating agents**

<b>Transfusion need</b>	<b>point</b>	<b>S-EPO</b>	<b>Point</b>
<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%

#### **Response criteria for evaluation of erythroid response**

- **Partial erythroid response (PER)**
  - In transfusion-dependent 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

#### **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

#### **Dosing of erythropoiesis stimulating agents**

- **Target hemoglobin level <120 g/l**
- **Induction phase:**
  - **EPO:** Start with EPO 30 000 U/week (reduce initial dose if impaired renal function or low body weight). Increase to 30 000 twice weekly if no response after 8 weeks. Doses higher than 60 000 U/week are not recommended .

- **DAR:** Start with 300 µg/14 days or 150 µg/week (reduce initial dose if impaired renal function or low body weight). Increase to 300 µg/week if no response after 8 weeks.
  - Aviod starting with 300 µg/week, since this may result in a rapid increase in Hb-level to supra normal levels for a period of time due to the extended half-life of DAR. Supra normal Hb-level is associated with increased risk of thrombosis.
- **G-CSF:** Add if no response to 8 weeks of full dose EPO or DAR. Start with 300 µg (or equivalent) once weekly, alternatively 120 µg 2-3 times a week. Aim at a clear rise in neutrophil count (to 6-10 x 10<sup>9</sup>/l). Maximum dose 300 µg x 3 times a week.
  - Long-acting G-CSF has not been evaluated in MDS and cannot be recommended.
- **Overdose:** If Hb-levels increase above upper normal limit then interrupt the growth factors and consider venesection; resume treatment at a lower dose when Hb falls below 120 g/l.
- **Maintenance phase:** In case of CER, decrease the dose every 8 weeks, by reducing the dose per injection or increasing the dosing interval (in particular when using DAR). Median dose of EPO is 30 000 U/week, although some patients maintain their response on weekly doses of 5000-10 000 U.
  - Monitor ferritin regularly, consider supplementation of oral or iv iron if ferritin falls below upper normal limit, in particular when there are signs of functional iron deficiency (low MCHC in absence of microcytosis).
- **Lost response:**
  - Evaluate for iron and vitamin deficiencies.
  - Increase the dose of EPO or DAR. If no response at maximum dose, then add G-CSF and evaluate after maximum of another 8-(16) weeks.
  - Bone marrow examination is recommended if response cannot be rescued or in case of clinical signs of disease progression (18-28 % of patients show signs of disease progression at time of lost response).

**Recommendation EPO**

Recommendation grade A, evidence level Ib.

**Recommendation EPO + G-CSF**

Recommendation grade A, evidence level Ib.

**Recommendation DAR±G-CSF**

Recommendation grade B, evidence level IIa.

**Immunosuppressive treatment****Background**

Several international studies have demonstrated response rates in the order of 30 % to immunosuppressive therapy (antithymocyte globulin (ATG) in some investigations combined with cyclosporine A (CyA)) in patients with MDS-SLD and MDS-MLD. Hypoplastic bone marrow, good and intermediate karyotype, HLA-DR15 positivity, young age, treatment within 2 years from diagnosis and short duration of red cell transfusion dependence<sup>23</sup> predict for a response to

immunosuppressive therapy in MDS patients. In aplastic anemia, ATGAM™ has been proven superior to other ATG, but this has not been investigated in MDS. Retrospectively, serum sickness was reported in 18 % and significantly higher with rabbit-ATG.

To date, there are no controlled data to support the addition of cyclosporine A to ATG treatment in MDS, although this combination has been shown to increase the response rate from 27 % to 51 % in a retrospective analysis<sup>23</sup>.

## ***Decision-making and treatment with ATG***

### **Indications for ATG**

- Patients with MDS-SLD and MDS-MLD with symptomatic anemia and/or thrombocytopenia and/or neutropenia with increased susceptibility to infections.

### **Positive criteria**

- Age: <70 years
- IPSS LR or INT-1/IPSS-R very low, low and intermediate
- Hypoplastic bone marrow
- HLA-DR15 positivity will strengthen the indication especially in patients >50 years and with a long duration of transfusion dependency.

### **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
- Prednisolone: During treatment with ATG, we recommend the addition of prednisolone day 1-24 (1 mg/kg/day d 1-10), then tapering the dose for the following 14 days until a complete stop.
- Prophylaxis with sulfamethoxazole/trimethoprim for 6 months is recommended.
- Consider prophylaxis with fluconazole and acyclovir.

**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.

## **Lenalidomide**

Lenalidomide is an immunomodulatory drug that targets the E3 ubiquitin ligase cereblon and induces drug-dependent degradation of specific substrates that are important for MDS cell survival. In transfusion dependent patients with lower risk MDS with del(5q) 43-56% achieve transfusion-independency and 23-57% show cytogenetic response. The response rates are higher with 10 mg/day 21/28 days compared to 5 mg continuous dosing, without added toxicity. Grade III-IV neutropenia and thrombocytopenia is seen in around 50% of patients. The response duration is around 2 years. The 5 year cumulative incidence of AML in treated patients is approximately 35%. Presence of TP53 mutation or marrow progenitors with strong p53 staining is associated with increased risk of progression<sup>24</sup>.

### ***Decision-making and treatment considerations***

- Eligible patients
  - Lower risk MDS with isolated del(5q) that have failed EPO or are not considered candidates according to the predictive model
  - No p53 alteration (TP53 mutation by deep sequencing of presence of >2% of marrow cells with strong p53 staining); such patients should be evaluated for alternative treatments due to their adverse prognosis and lenalidomide should only be considered in frail patients where no suitable alternative is available
- Non eligible patients
  - Candidates for allo SCT; if lenalidomide is given in selected transplant candidates it should only be in the absence of p53 alterations, with careful monitoring for signs of disease progression.
- Dosing
  - Repeated courses of 10 mg daily for 21 days followed by a 7 day break.
  - In elderly frail patients or patients with renal impairment consider 5 mg 21 of 28 days.
- Prior to lenalidomide treatment, patients should be informed about the increased risk of other malignancies observed in multiple myeloma patients
- Lenalidomide is not recommended for non del(5q) MDS or advanced MDS, unless in a clinical trial
- Sexually active, fertile patients must use effective contraception

### **Recommendation Lenalidomide**

Recommendation grade A, evidence level 1b.

## **Allogeneic stem cell transplantation (SCT) in MDS**

### ***Background***

Allogeneic stem cell transplantation is the only known curative treatment option in patients with MDS<sup>25</sup>. Published registry data for MDS show disease free survival rates between 35 and 40 %, transplant related mortality (TRM) between 5-20 % depending on donor type, and relapse rates (RR) 20-30 %<sup>26,27</sup>. Several non-randomized studies have compared reduced intensity conditioning (RIC) transplantation with conventional myeloablative conditioning (MAC) transplantation<sup>26-28</sup>.

Most of the studies describe similar overall survival. The causes of treatment failure, however, are different with more relapses in RIC SCT patients, but higher TRM in patients receiving MAC. Results have improved during the last decade and more elderly patients have been possible to transplant due to better matched unrelated donors and with the introduction of RIC and reduced toxicity conditioning (RTC). Promising results have been described with the RTC-regimen Treosulfan-Fludarabine with a reduced RR compared to standard RIC without a corresponding higher TRM compared to conventional MAC. In the study by Ruutu et al of 45 MDS –patients the 2 years relapse rate was 16 % , the non-relapse mortality 17 % and the OS 71 % <sup>29</sup>.

Poor risk factors for TRM:

- High age
- Advanced disease stage
- Therapy related MDS
- Sub optimally matched unrelated donor
- Comorbidities.

Risk factors for relapse:

- High age
- Advanced disease stage
- Poor risk cytogenetics.
- Disease duration
- Severe marrow fibrosis <sup>30</sup>.
- Somatic mutations in *ASXL1*, *RUNX1* and *TP53*, *EZH2* and *ETV6* seem to be independent prognostic factors.

Large retrospective studies have found that the percentage of bone marrow blasts at the time of transplantation significantly influences on prognosis, but selection bias and the mortality related to cytoreduction should be taken into account<sup>31</sup>.

## ***Decision making and treatment***

### **Indications (sibling or unrelated)**

- Age: All fit patients without comorbidities should be considered for allogeneic SCT. The indication should be assessed in association with donor availability, eventual co-morbid conditions and functional status (see comorbidity index).
- IPSS INT-1, INT-2, and HR. In INT-1, IPSS-R can help to identify candidates for stem cell transplantation. Somatic mutations should in some cases be considered. Poor risk factors may be identified in lower risk and intermediate risk patients, indicating a need for an early SCT.

## **Cytoreductive chemotherapy prior to SCT in patients with intermediate and high risk (according to IPSS-R), high risk MDS (according to IPSS) and MDS/AML**

Cytoreductive therapy is usually given before SCT, but the value is not established due to lack of randomized trials and conclusive retrospective data<sup>25,28-30</sup>. However, induction chemotherapy significantly increases the risk of mortality and morbidity, which may prevent SCT.

- Intermediate risk patients according to IPSS-R with increasing blast counts  $\geq 10\%$  should be considered for cytoreductive therapy.
- Treatment should be determined in close collaboration with the local transplant team and usually involves azacitidine or AML like chemotherapy.

### Decision making

- At diagnosis **always** consider if the patient is a candidate for allogeneic stem cell transplantation. 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-associated disorders) that 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 caretaking physician and the transplant unit.
- Evaluate patient for potential comorbidities (according to Sorror, Blood 2013, see next page).
- 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 (possibly familial) disorder as the patient and to be screened for it if suspected.
- If no sibling available, search for unrelated donor.
- Other alternative donors (cord blood graft or haploidentical graft) might be considered depending on age, disease, and co-morbidity.
- All transplant related procedures (conditioning, immunosuppression and supportive care) should be performed according to local guidelines. However, it is recommended to use a limited number of conditioning regimens. The selection of regimens should be discussed within each country with the transplant teams.

### Recommendation regarding allogeneic SCT

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 that has been shown in many (but not all studies) to predict non-relapse mortality and survival. The HCT-CI has been updated and is available on the web (<http://www.hctci.org/>)<sup>32</sup>. It is recommended to evaluate a potential transplantation candidate with HCT-CI prior to referral. The higher the HCT-CI, the higher is the risk for non-relapse mortality (transplantation related mortality) and the lower the overall survival. It has also been suggested that Karnofsky scores together with HCT-CI gives better prediction on the risk for TRM than either used alone.

**Table 9. HCT-CI**

Comorbidity	Definition of comorbidity	HCT-CI weighted score
-------------	---------------------------	-----------------------

Arrhythmia	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 hypoglycemic 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 <sup>2</sup>	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 <sub>1</sub> 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV <sub>1</sub> ≤ 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
SUM		—

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.

### **Azacitidine**

#### ***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 hematopoietic stem cell transplantation.

A randomized 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<sup>33</sup>. 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 percent of azacitidine treated patients responded with CR or PR. The benefit of azacitidine 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)<sup>33-39</sup>. A total of 50% responded (CR, PR and hematological improvement = HI) to azacitidine-treatment and first response was seen in 91% of the responders within 6 cycles and best response was seen in 48% of the responders within 12 cycles, underscoring the importance of continuing treatment even if no response can be observed after a few courses<sup>34,40</sup>. Of importance is that even patients with HI only, also had an OS benefit compared to BSC i.e. CR/PR is not a prerequisite for azacitidine-treatment benefit (paradigm shift)<sup>33,40,41</sup>..

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<sup>42,43</sup>.

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.

## ***Decision making and treatment***

### **Indication**

- Mainly indicated in patients who are not candidates for curative treatment, although azacitidine can also be considered when choosing 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.
- Expected survival exceeding 3 months.

### **Azacitidine treatment**

- Azacitidine 75 mg/m<sup>2</sup> sc d 1-7 repeated every 28 days. (alternative dosing schedules can be considered: 100 mg/m<sup>2</sup> sc d 1-5 or 75 mg/m<sup>2</sup> sc d 1-5 + 8-9).
- Continue treatment unless obvious signs of progression. Obvious signs of improvement are rarely observed after only 1 to 2 courses of treatment.
- Myelosuppression is very common especially during the first courses and should not lead to un-necessary pausing or dose reductions unless threatening cytopenic complications or intolerance. The use of G-CSF and/or prophylactic antibiotics could be considered.
- Evaluate response (bone marrow assessment) after 6 courses unless there is overt progression or indications of overdosing earlier. If SCT is planned, evaluate after 3 cycles or earlier if progression is suspected. Allow sufficient time (5-6 weeks) after last course before marrow evaluation (include biopsy), 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 azacitidine. It may be useful to make an 8 weeks pause after cycle 6 to see if recovery occurs.
- It is generally recommended to continue treatment until clear signs of loss of response or progression. Fragile and elderly patients may not tolerate treatment and may experience

treatment induced marrow suppression. In such case the dose can be decreased or the dose interval increased to 5 weeks.

**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<sup>44-50</sup>. 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  $<4 \times 10^9/l$  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, i.e. 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<sup>51,52</sup>. Hence, no recommendation can be made as to the 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), IPSS-R intermediate 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, i.e. normal s-LDH and/or WBC  $<4.0 \times 10^9/L$ , 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.
- If 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

### *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 with melphalan or Ara-C 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<sup>53-55</sup>.

- 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**

Recommendation grade B, evidence level IIb.

### **Low-dose cytosine arabinoside**

One large randomized 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<sup>56-58</sup>. 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 azacitidine<sup>33</sup>.

- 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<sup>2</sup>/day sc, for 2-8 weeks. Maintenance treatment might be given to responders.

### **Recommendation**

Recommendation grade A, evidence level Ib.

## Chronic myelomonocytic leukemia (CMML)

### **Background**

Chronic myelomonocytic leukemia is a rare disease with an incidence of 3/100.000/year in the population > 60 years, male: female ratio is 2:1, median age at presentation is 65-75 years. 15-20 % transform to AML. The disease has both myeloproliferative and myelodysplastic features. In 1994, the FAB group proposed to separate CMML in a proliferative form (CMML-MP) with white cell counts >13 x 10<sup>9</sup>/L, and a dysplastic form (CMML-MD) with white cell counts below 13 x 10<sup>9</sup> /L. The WHO 2016 classification divides CMML into three groups based on the number of blasts: CMML-0: < 2 % blasts (including promonocytes) in PB and < 5 % blasts (including promonocytes) in BM), CMML-1: 2-4 % blasts (including promonocytes) in PB and 5-9 % blasts (including promonocytes) in BM), CMML-2: 5-19 % blasts (including promonocytes) in PB and 10-19 % blasts (including promonocytes) in BM). **Diagnostic criteria (according to WHO 2016): See Table 3.**

In 20-40 % of cases, clonal abnormalities can be found, 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. *SRSF2* mutations are seen in 40-45 % and *ASXL1* mutations in 50 % of the patients and both mutations seem to confer a worse prognosis.

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

CMML specific scoring system (CPSS, Such et al<sup>59</sup>), Table 10, defines 4 important prognostic factors including WHO subtype, FAB subtype, CMML-specific cytogenetic risk classification and transfusion dependency. Patients could be divided into 4 risk groups differing in OS and AML evolution; low risk (0 points), intermediate-1 (1 point), intermediate-2 (2-3 points) and high risk (4-5 points). The median overall survival (OS) for low, intermediate-1, intermediate-2 and high risk were: 61, 31, 15 and 9 months.

**Table 10. CPSS score**

Prognostic variable	Points		
	0	1	2
Blasts (%)	<10 % in BM and < 5 % in PB	10-19 % in BM or 5-19 % in PB	
White cell count	Up to 13 x 10 <sup>9</sup> /L	> 13 x 10 <sup>9</sup> /L	
Karyotype <sup>o</sup>	Low risk	Intermediate	High risk
Transfusion dependency	No	Yes	

Abbreviations: BM = bone marrow. PB = peripheral blood. <sup>o</sup> Low risk: normal, -Y, del(5q), del(20q). High risk: trisomy 8, complex (≥ 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. Red blood cell (RBC) ransfusion dependency defined as having 1 RBC transfusion every 8 weeks over a period of 4 months.

**Table 11. CMML genetic score and CPSS-Mol**  
(Elena et al<sup>60</sup>)

Variables and prognostic score values of the CMML genetic score

	CPSS cytogenetic risk group	<i>ASXL1</i>	<i>NRAS</i>	<i>RUNX1</i>	<i>SETBP1</i>
<b>Variable score</b>					
<b>0</b>	Low	Unmutated	Unmutated	Unmutated	Unmutated
<b>1</b>	Intermediate	Mutated	Mutated	Na	Mutated
<b>2</b>	High	Na	Na	Mutated	Na
<b>Genetic risk group</b>	<b>Score</b>				
<b>Low</b>	0				
<b>Intermediate-1</b>	1				
<b>Intermediate-2</b>	2				
<b>High</b>	≥3				

Cytogenetic risk groups are defined according to Such et al<sup>59</sup>: low, normal, and isolated -Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

Variables and prognostic score values of the CPSS-Mol

	Genetic risk group	BM blasts	WBC count	RBC transfusion dependence
<b>Variable score</b>				
<b>0</b>	Low	< 5 %	< 13x10 <sup>9</sup> /L	No
<b>1</b>	Intermediate-1	≥ 5 %	≥ 13x10 <sup>9</sup> /L	Yes
<b>2</b>	Intermediate-2	Na	Na	Na
<b>3</b>	High	Na	Na	Na
<b>CPSS-Mol risk group</b>	<b>Score</b>			
<b>Low</b>	0			
<b>Intermediate-1</b>	1			
<b>Intermediate-2</b>	2			
<b>High</b>	≥4			

Genetic risk groups are defined as reported in the table above.

RBC transfusion dependency is defined according to Malcovati et al<sup>61</sup> and Such et al.<sup>59</sup>

This model was able to identify 4 risk groups with significantly different OS (HR = 2.69, *P* < .001) and cumulative incidence of leukemic evolution (HR = 3.84, *P* < .001) (median survival not reached, 64, 37, and 18 months; 48-month cumulative incidence of AML evolution of 0%, 3%, 21%, and 48% for the low, intermediate-1, intermediate-2, and high-risk group, respectively).<sup>60</sup> The learning and validation cohorts consisted of 214 and 260 CMML patients, respectively<sup>60</sup>.

## Algorithm for treatment of patients with CMML

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.

1. Consider allogeneic SCT for both CMML 1 and CMML 2.
2. Patient with CMML 2 (10-19 % marrow blasts and promonocytes) and leukocyte count less than  $13 \times 10^9/L$ : Azacitidine.
3. Patient with CMML 2 (10-19 % marrow blasts and promonocytes) and leukocyte count more than  $13 \times 10^9/L$  but not severely elevated leukocyte counts: Azacitidine treatment can be effective (less evidence for its benefit). Alternatively hydroxyurea or AML-like chemotherapy may be given.
4. Patient with CMML 1 (5-9 % bone marrow blasts and promonocytes), leukocytes less than  $13 \times 10^9/L$  and high- risk cytogenetics: Treatment with azacitidine should be considered if candidate for allogeneic stem cell transplantation. Otherwise: Wait and see. Can be treated with EPO according to recommendations for other low risk MDS.
5. Patient with CMML 0 (< 5 % blasts) or CMML 1 (5-9 % bone marrow blasts and promonocytes) and leukocytes more than  $13 \times 10^9/L$ : Hydroxyurea if symptomatic, EPO if anemia.

## **Allogeneic stem cell transplantation in CMML**

Chronic myelomonocytic leukemia is a challenging disease being difficult to cure even with allogeneic stem cell transplantation. CPSS<sup>59</sup> was validated in 209 transplanted patients by Duong and colleagues in 2015. There was a difference in 5 years disease-free survival (DFS) between low/int-1 and int-2/high risk CPSS (26 % vs 14 %) and OS (44 % vs 18 %) respectively. Mortality from higher CPSS scores was more often related to relapse than with lower scores. Other factors that significantly predicted outcome were performance status (better when > 90 %) and graft source (better for peripheral stem cells). The long term DFS was 26 % in the whole population and only 14 % in int-2-/high-risk<sup>62</sup>. In an EBMT-study with 513 CMML patients 4-years, non-relapse mortality was 41 %, RR 32 %, relapse-free survival 27 % and OS 33 %<sup>63</sup>. The only significant prognostic factor for survival in a multivariate analysis was the presence of complete remission at HSCT. Therefore, transplantation early after diagnosis or after achievement of the best possible remission with either chemotherapy is recommended<sup>63</sup>.

Somatic mutations also seem to be independent prognostic factors for CMML. An updated prognostic score of CPSS (CPSS mol) has recently been presented in Blood<sup>60</sup>. CPSS mol incorporates mutations in *RUNX*, *NRAS*, *ASXL1* and *SETBP* in the prognostic system (Table 11).

### **Indications for Allogeneic stem cell transplantation**

- Fit patients without severe comorbidities CMML-2 or CMML-1 with at least Int-1 score. Somatic mutations should be considered in some cases.
- Patients with CMML-2 should receive therapy with the aim to obtain the best possible remission before SCT.

## Azacitidine

### **Background**

Both FDA and EMEA have approved 5-azacitidine for treatment of CMML with 10-29% marrow blasts without a myeloproliferative disorder (leukocyte counts below  $13 \times 10^9/l$ ).

One retrospective single center study investigated effects of azacitidine in CMML with leukocyte counts below and above  $13 \times 10^9/L$ . The OR was 39%, and it seemed to be better response in the MDS-CMML-group compared to the MPD-CMML-group; although the differences were not significant.

### **Recommendation:**

Recommendation grade A, evidence level 1b.

## Hydroxyurea

One randomized trial with Hydroxyurea (HU) vs. Etoposide (VP 16) showed superiority in response (60 % vs.36 %). Survival in the HU arm was 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 with azacitidine.

If the patient does not respond to HU or presents signs of progression of the disease, consider azacitidine as second-line treatment (see below).

### **Recommendation:**

Recommendation grade B, level IIa.

## **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.

## 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*

Decitabine is another hypomethylating agent that, similar to azacitidine causes demethylation of genes and re-expression of i.e. cell cycle control proteins.

A large phase II study showed that decitabine had significant effects in high-risk MDS, and that major cytogenetic responses could be observed in 19/61 of responding patients. 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 center 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.

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.

### **Status**

Decitabine is approved by FDA for both MDS and AML. Decitabine is also commercially available in most countries in Europe for the treatment of AML in the elderly.

### **Indication**

- IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other possible treatment modalities have failed), especially in case of intolerance to azacitidine.
- Not candidates for curative treatment or induction chemotherapy.

### **Treatment with Decitabine**

- Decitabine 15 mg/m<sup>2</sup> by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks. Alternatively give 20 mg/m<sup>2</sup>, 1 hour intravenous infusion for 5 consecutive days, repeated every 4 weeks.
- Evaluate response (bone marrow assessment) after 4-6 courses unless there is overt progression earlier.
- Continue treatment until progression, even in the absence of hematological improvement.

**Recommendation:** Not recommended for treatment of MDS, unless azacitidine intolerance.

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

See [www.nmds.org](http://www.nmds.org)

### **Disclosure statement**

AOK: Covered congress/travel expenses by Celgene, Advisory board - Celgene

LC: Honorarium for lectures - Ariad

ID: Covered congress/travel expenses by Celgene, Advisory board - Celgene

FE: Expert statement for Celgene, congress/travel expenses covered by Amgen and Novartis

EE: None

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EP: None

KRJ: Covered congress/travel expenses, Advisory board - Celgene and Novartis, Honorarium for lectures/meeting chairperson - Celgene

LS: None

**Table 12. Genes frequently mutated in MDS.**

Gene	Function	Target regions	Types of pathogenic variants	Main hotspots	Mutational frequency <sup>4</sup>	Mutational frequency <sup>5</sup>	Comment	Ref.
<i>ASXL1</i>	Chromatin modification	Exon 13	Nonsense and frame-shift variants	p.E635fs*; p.G646fs	23 %	14 %	Shortened survival <sup>8,64,65</sup> . Associated with unfavorable clinical outcome in all myeloid neoplasms (MDS, MDS/MPN, MPN).	8,64-69
<i>BCOR</i>	Transcriptional regulation	Total coding region	Nonsense and frame-shift variants		4 %	5 %	Shortened survival <sup>70</sup> . Frequent in aplastic anemia <sup>71</sup> .	70-72
<i>CALR</i>	Signal transduction	Exon 9	Indels in exon 9	p.L367fs*46; p.K385fs*47			MPN	
<i>CSFR3</i>	Signal transduction	Exon 14 and 17	Missense (E14) and truncating (E17) variants	p.T618I			Strictly associated with CNL, found in a subset of patients with aCML.	73-76
<i>CBL</i>	Signal transduction	Exon 8 and 9	Multiple types of pathogenic variants		5 %	4 %	Shortened survival <sup>8</sup> .	8,77-81
<i>DNMT3A</i>	DNA methylation	Exon 7 to 23	Multiple types of pathogenic variants mainly missense	p.R882	13 %	11 %	Shortened survival <sup>82</sup> .	7,82
<i>ETV6</i>	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants	PNT and ETS domains	2 %	1 %	Shortened survival <sup>8</sup> .	8,83,84
<i>EZH2</i>	Chromatin modification	Total coding region	Multiple types of pathogenic variants	SET-domain (p.R690)	6 %	5 %	Shortened survival <sup>8,64</sup> .	8,64,85,86
<i>GATA1</i>	Transcriptional regulation	Exon 2	Multiple types of pathogenic variants				AML in Down syndrome	
<i>GATA2</i>	Transcriptional regulation	Exon 2 to 6	Multiple types of pathogenic variants	exon 5 and 6 (ZF1 and ZF2 domains)			Familial AML/MDS.	87-91
<i>IDH1</i>	DNA methylation	Exon 4	Missense variants	p.R132	3 %	3 %	Shortened survival <sup>92</sup> .	92-94
<i>IDH2</i>	DNA methylation	Exon 4	Missense variants	p.R140; pR172	4 %	4 %		92,93,95,96
<i>JAK2</i>	Signal transduction	Exon 14 and 12	V617F (E14) and in-frame del/ins or missense variants in (E12)	p.V617F	5 %	5 %	No impact on survival <sup>8,64</sup> .	8,64

<b>KIT</b>	Signal transduction	Exons 8-14, Exon 17	Multiple types of pathogenic variants	p.D816	1 %	2 %	AML	
<b>KRAS</b>	Signal Transduction	Exon 2 and 3	Missense variants	p.D12, p.D13, p.D61	3 %	2 %		
<b>MPL</b>	Signal transduction	Exon 10	Missense variant	p.W515L	3 %	2 %	MPN	
<b>NF1</b>	Signal transduction	Total coding region	Multiple types of pathogenic variants		3 %	4 %	Familial cases, JMML	97
<b>NPM1</b>	Signal transduction	Exon 12	Insertions	p.W288fs*12	1 %	1 %	AML	
<b>NRAS</b>	Signal Transduction	Exon 2 and 3	Missense variants	p.D12, p.D13,p.D61	4 %	3 %	Shortened survival	8
<b>PHF6</b>	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants	Mainly truncating variants and missense variants in PHD2 domain (p.R274Q and p.K235E)	3 %	2 %		98
<b>PTPN11</b>	Signal transduction	Exons 2, 3, 4, 7, 8, 12, and 13	Missense mutations	N-SH2 and PTP domains	1 %	1 %	JMML and childhood AML (both acquired or inherited) but rare in adults with MDS (1%)	99-101
<b>RAD21</b>	Cohesin complex		Multiple types of pathogenic variants but mainly truncating variants				2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	102-104
<b>RUNX1</b>	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants		11 %	8 %	Shortened survival <sup>8</sup> . Associated with unfavorable clinical outcome.	8,64,68
<b>SETBP1</b>		Exon 4	Missense variants	p.S867;p.D868; p.S869; p.G870; p.I871	4%-9%		Associated with poor overall survival and high risk of leukaemic evolution	69,105-109
<b>SF3B1</b>	RNA splicing	Exons 11 to 16	Missense variants	p.K700; p.K666; p.H662;p.H662;p.R625; pE622	33 %	25 %	Longer survival <sup>110</sup> . No impact on survival <sup>64,111</sup> . Associated with good overall survival and low risk of leukemic evolution.	107,112-116
<b>SMC1A</b>	Cohesin complex	Exons 2, 11, 16 + 17	Mainly missense variants				<1% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	102-104

<b>SMC3</b>	Cohesin complex	Exons 10, 13, 19, 23, 25 + 28	Multiple types of pathogenic variants				2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	102-104
<b>SRSF2</b>	RNA-splicing	Exon 1	In-frame deletions and missense variants	p.P95_R102del; p.P95	18 %	15 %	Shortened survival <sup>112,115,117</sup> . No impact on survival <sup>64</sup> . Associated with poor overall survival and high risk of leukaemic evolution.	112,113,115-124
<b>STAG2</b>	Cohesin complex	Total coding region	Multiple types of pathogenic variants, mainly truncating variants		8 %	5 %	2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	Shortened survival <sup>104</sup>
<b>TET2</b>	DNA methylation	Total coding region	Multiple types of pathogenic variants		36 %	26 %	No impact on survival <sup>8,64,125</sup> . Shortened survival after transplant <sup>7</sup> . No impact on overall survival, may predict response to hypomethylating agents.	35,125-131
<b>TP53</b>	DNA repair	Exon 3 to 11	Multiple types of pathogenic variants		6 %	5% (17% in del(5q))	Shortened survival <sup>8,64</sup> after transplant <sup>127</sup> . Poor response	8,64,68,127,132,133
<b>U2AF1</b>	RNA splicing	Exon 2 and 6	Missense variants	p.S34; p.R156; p.Q157	8 %	6 %	No impact on survival <sup>64</sup> . Shortened survival <sup>107</sup> . Associated with high risk of leukemic evolution.	112,115,123,134,135
<b>WT1</b>	DNA methylation	Exon 7 and 9	Multiple types of pathogenic variants		1 %	1 %	AML	
<b>ZRSR2</b>	RNA splicing	Total coding region	Multiple types of pathogenic variants, mainly truncating variants.		8 %	5 %	No impact on survival <sup>115</sup> . Shortened survival in ZRSR2mut/TET2wt. <sup>112</sup>	112,115,116,136

**Table 13. Main hereditary myeloid malignancy syndromes**

Syndrome	Gene	Ref.:
Thrombocytopenia 2	<i>ANKRD26</i>	137
Thrombocytopenia 5	<i>ETV6</i>	138
FPD/AML	<i>RUNX1</i>	139-141
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Telomere syndromes with familial MDS/AL presentation	<i>TERC, TERT</i>	149,150
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