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

Nordic MDS Group

Issue 8

7th update, 30th of December 2015
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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, and also of CMML, to 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.

Writing committee

Astrid Olsnes Kittang (chair), Lucia Cavelier, Ingunn Dybedal, Freja Ebeling, Lone Friis, Hege Garelius, Mette Skov Holm, Martin Jädersten, Lars Kjeldsen, Eva Hellström Lindberg, Per Ljungman, Jan Maxwell Nørgaard, Lars Nilsson, Eira Poikonen, Klas Raaschou-Jensen, and Leonie Saft.

Contact information

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News in issue 8

Since degree of anemia is included in IPSS-R, we have removed WPSS-score from the prognosis-section. The section on allogeneic stem cell transplantation in MDS and CMML is updated. More emphasis is put on p53-mutation status in decision-making and treatment. Thalidomide has been removed from treatment alternatives. A new WHO-classification for MDS is expected in 2016, and will then be included. A section on thrombocytopenia has been added.

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

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

B) Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia, Ib</td>
<td>Required: At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation</td>
</tr>
<tr>
<td>B</td>
<td>IIa, Iib, III</td>
<td>Required: Availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>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</td>
</tr>
</tbody>
</table>
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. A chromosome analysis is also an essential part of the diagnostic process, which should distinguish MDS from other 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 in the presence of a positive family history, concomitant physical abnormalities (ex 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) and GATA2-mutations.

Diagnostic work-up of MDS:

Patient history and examination:
This should include family history, prior chemotherapy and irradiation, occupational exposure, alcohol-use, 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) and reticulocyte count. For dysplasia, see below under bone marrow evaluation.
- Measure RBC-folate/S-folic acid, and serum cobalamin, homocystein and methylmalonic acid.
- Ferritin, LDH, bilirubin, haptoglobin, DAT (Coombs test), ALAT, ASAT, alkaline phosphatase, albumin, uric acid, creatinin, S-erythropoietin, S-protein electrophoresis.
- Screening for HIV, hepatitis B and C. Parvovirus B19 (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.

Bone marrow analysis:
A diagnosis of MDS usually necessitates repeated bone marrow examinations a few weeks or months apart in order to firmly establish the diagnosis and to identify cases with rapid disease progression. In case of poor cytogenetics, severe pancytopenia or increased blast counts treatment should start immediately if indicated, and not be postponed by an additional bone marrow examination. We recommend evaluation of bone marrow and peripheral blood smears for the assessment of cytormorphological dysplasia and blast counts together with a histological examination according to the WHO 2008 classification.

Bone marrow aspirate and biopsy. For significant dysplasia, dysplastic features should be present in at least 10% of cells within erythro- and/or granulopoiesis. Significant megakaryocyte dysplasia is
also defined by the 10% threshold based on the evaluation of at least thirty megakaryocytes in smears or sections

- For the assessment of blasts, at least 500 bone marrow cells (expressed as a percentage of all nucleated cells, always including nucleated red cells) and 200 cells in a peripheral blood smear should be evaluated, and optimal staining of blood and marrow slides is important. The presence of pseudo-Pelger-Huët neutrophils, hypogranulated 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.
- Immunohistochemistry for CD34 and p53 is recommended in the diagnostic work-and follow-up of all suspected MDS. The presence of cells with strong nuclear p53 IHC staining may indicate an underlying TP53 mutation and should be followed in sequential biopsies.

In some patients clinically relevant cytopenia(s) can be present without any other obvious cause, significant dysplasia or bone marrow blast increase. This condition has provisionally been defined as ICUS (Idiopathic Cytopenias of Undetermined Significance). These patients should be carefully monitored since a fraction of them will develop decisive MDS criteria. Importantly, a diagnosis of MDS can be made in the absence of significant dysplasia or bone marrow blast increase if typical chromosomal abnormalities are present or develop during the observation period.

**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/HCV/HBV/Parvovirus B19/CMV/EBV-infection
- Anemia of chronic disorders (chronic infection, inflammation, cancer)
- 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), paroxysmal nocturnal hemoglobinuria (PNH) and hairy cell leukemia.
**Classifications** (the revised WHO classification will be published Q2 2016 and will then be included)

The Nordic MDS group recommends classification according to WHO (2008) only

**WHO 2008 classification of MDS**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenias with unilineage dysplasia (RCUD)</td>
<td>Unicytopenia or bicytopenia¹</td>
<td>Unilineage dysplasia: ≥ 10% of the cells of the affected lineage are dysplastic</td>
</tr>
<tr>
<td>Refractory anaemia (RA)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td>Refractory neutropenia (RN)</td>
<td></td>
<td>&lt;15% of the erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td></td>
<td>No blasts</td>
<td>≥ 15% of erythroid precursors are ring sideroblasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenia(s)</td>
<td>Dysplasia in ≥ 10% of cells in two or more myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes)</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts (&lt;1%)²</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1x10⁹/l monocytes</td>
<td>±15% ring sideroblasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenia(s)</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>&lt;5% blasts</td>
<td>5-9% blasts³</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1x10⁹/l monocytes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenia(s)</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>5-19% blasts</td>
<td>10-19% blasts</td>
</tr>
<tr>
<td></td>
<td>Auer rods ≥³</td>
<td>Auer rods²</td>
</tr>
<tr>
<td></td>
<td>&lt;1x10⁹/l monocytes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic syndrome – unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines</td>
</tr>
<tr>
<td></td>
<td>≥ 1% blasts²</td>
<td>&lt;5% blasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anaemia</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei</td>
</tr>
<tr>
<td></td>
<td>Usually normal or increased platelet count</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts (&lt;1%)</td>
<td>Isolated del(5q) cytogenetic abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No auer rods</td>
</tr>
</tbody>
</table>

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.

³Cases 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelomonocytic leukaemia (CMML)</td>
<td>Peripheral blood monocytosis &gt; 1x10^9/l No BCR/ABL-1 fusion gene &lt;20% blasts</td>
<td>Dysplasia in one or more myeloid lineage^1^ &lt;20% blasts. Blasts include myeloblasts, monoblasts and promonocytes. No rearrangement of PDGFRA or PDGFRB</td>
</tr>
<tr>
<td>Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)</td>
<td>Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophil precursors ≥10% of leukocytes Blasts &lt;20% No BCR-ABL1 fusion gene No rearrangement of PDGFRA or PDGFRB Minimal basophilia Monocytes &lt; 10% of leukocytes</td>
<td>Neutrophil dysplasia with or without dysplastic lineages &lt;20% blasts</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukaemia (JMML)</td>
<td>Peripheral blood monocytosis &gt;1x10^9/l &lt;20% blasts Usually WBC &gt; 10x10^9/l</td>
<td>&lt;20% blasts. Evidence of clonality</td>
</tr>
<tr>
<td>Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)</td>
<td>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</td>
<td>Mixed MDS and MPN features &lt;20% blasts</td>
</tr>
</tbody>
</table>

^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

^2^If myelodysplasia is minimal or absent, CMML can still be diagnosed if the other requirements are met, and there is an acquired clonal cytogenetic or molecular genetic abnormality present in the bone marrow cells. Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

^3^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.

^4^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 excludes s/t-MDS and CMML with leukocyte count >12 x10⁹/l. Importantly, IPSS also underestimates the prognostic impact of karyotype relative to the percentages of blast cells in the bone marrow. This has been changed in the recently published revised IPSS score, where unfavourable cytogenetics weigh more than an elevated percentage of marrow blasts.

**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. Follow this link to perform online IPSS scoring: [http://nmds.hematology.dk/index.php/guidelines](http://nmds.hematology.dk/index.php/guidelines)

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

**All patients (n=816):**

**Patients below age 60 (n=205):**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score</th>
<th>Median survival (years)</th>
<th>Time to AML transformation (for 25% in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0</td>
<td>11.8</td>
<td>&gt;9.4</td>
</tr>
<tr>
<td>INT-1</td>
<td>0.5-1.0</td>
<td>5.2</td>
<td>6.9</td>
</tr>
<tr>
<td>INT-2</td>
<td>1.5-2.0</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>High risk</td>
<td>≥2.5</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Score values**

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>&lt;5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype°</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopoenias*</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

° 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 10⁹/l, platelets <100 x 10⁹/l.
Revised IPSS (IPSS-R)

A total of 7012 patients from 5 different MDS databases formed the basis of the IPSS-R. As in IPSS, only patients not receiving disease modifying treatments are included, all with WBC < 12 x 10^9/l and neutrophils < 8 x 10^9/l. IPSS-R evaluates the prognosis at diagnosis (as in IPSS) and separates patients into 5 risk groups. Cytogenetics, blast percentage and degree of cytopenias remained the basis of the revised system. Five cytogenetic risk groups are defined. Prognostic evaluation by IPSS-R is recommended particularly in allogeneic transplant candidates.

Follow this link to perform online IPSS-R scoring: http://nmds.hematology.dk/index.php/guidelines

IPSS-R prognostic groups and score values

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

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
</tr>
<tr>
<td>BM blasts, %</td>
<td>≤2%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Risk score</th>
<th>Patients (%)</th>
<th>Survival (median, y)</th>
<th>AML transformation (25% of patients, y), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤1.5</td>
<td>19</td>
<td>8.8</td>
<td>NR (14.5-NR)</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
<td>38</td>
<td>5.3</td>
<td>10.8 (9.2-NR)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3-4.5</td>
<td>20</td>
<td>3.0</td>
<td>3.2 (2.8-4.4)</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
<td>13</td>
<td>1.6</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6</td>
<td>10</td>
<td>0.8</td>
<td>0.73 (0.7-0.9)</td>
</tr>
</tbody>
</table>
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.

Similarly, 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. It is important to emphasise that IPSS-R is not yet included in any of the therapeutic schedules, although we recommend to use it as a tool for risk stratification.

IPSS-R Intermediate risk

As survival is of predominant concern to patients and caregivers, Greenberg et al. suggested placement of IPSS-R Intermediate patients into the lower-risk group regarding their potential therapeutic management. However, given the distinctiveness of this patient category, it is warranted to assess these patients within both lower- and higher-risk treatment protocols. Use of additional differentiating features could be of particular value for categorization of these patients.

Additional prognostic factors

- **Comorbidity:** The prognostic importance of comorbidity has been systematically evaluated by Della Porta and co-workers and a time-dependent myelodysplastic syndrome-specific comorbidity index (MDS-CI) developed. Cardiac, liver, renal, pulmonary disease and solid tumors were found to independently affect the risk of non-leukemic death.

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

- **Mutations:** Point mutations in TP53, EZH2, ETV6, RUNX1, NRAS and ASXL1 have been associated with poor prognosis in several publications. Spliceosomal mutations in SRSF2 and U2AF1 have as well been associated with poor prognosis, while SF3B1 mutations seem to be associated with a trend towards longer survival. 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 may be considered in borderline cases, especially in candidates for allogeneic stem cell transplantation.

Recommendation for diagnosis and prognosis

- All patients should be classified according to WHO 2008 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.
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Response criteria (response must last at least 4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>Bone marrow ≤ 5% myeloblasts with normal maturation of all cell lines</td>
</tr>
<tr>
<td></td>
<td>Persistent dysplasia will be noted</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood:</td>
</tr>
<tr>
<td></td>
<td>* Hb ≥ 110 g/L,</td>
</tr>
<tr>
<td></td>
<td>* Platelets ≥ 100 x 10^9/L,</td>
</tr>
<tr>
<td></td>
<td>* Neutrophils ≥ 1.0 x 10^9/L,</td>
</tr>
<tr>
<td></td>
<td>* Blasts 0%.</td>
</tr>
<tr>
<td>Partial remission</td>
<td>All CR criteria if abnormal before treatment except:</td>
</tr>
<tr>
<td></td>
<td>Bone marrow blasts decreased by ≥ 50% over pre-treatment but still &gt; 5%</td>
</tr>
<tr>
<td></td>
<td>Cellularity and morphology not relevant</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>BM ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood: if HI responses, they will be noted in addition to marrow CR</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Failure to achieve at least PR, but no evidence of progression for &gt; 8 wks</td>
</tr>
<tr>
<td>Failure</td>
<td>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</td>
</tr>
<tr>
<td>Relapse after CR or PR</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td></td>
<td>* Return to pretreatment BM blast percentage</td>
</tr>
<tr>
<td></td>
<td>* Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets</td>
</tr>
<tr>
<td></td>
<td>* Reduction in Hb concentration by ≥ 15 g/L or transfusion dependence</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td>Complete: Disappearance of the chromosomal abnormality without new ones</td>
</tr>
<tr>
<td></td>
<td>Partial: At least 50% reduction of the chromosomal abnormality</td>
</tr>
<tr>
<td>Disease progression</td>
<td>≥ 50% increase in blasts</td>
</tr>
<tr>
<td></td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>* At least 50% decrement from maximum remission/response in granulocytes or platelets</td>
</tr>
<tr>
<td></td>
<td>* Reduction of Hb by ≥ 20g/L</td>
</tr>
<tr>
<td></td>
<td>* Transfusion dependence</td>
</tr>
<tr>
<td>Survival</td>
<td>Endpoints:</td>
</tr>
<tr>
<td></td>
<td>* Overall: death from any cause</td>
</tr>
<tr>
<td></td>
<td>* Event free: failure or death from any cause</td>
</tr>
<tr>
<td></td>
<td>* PFS: disease progression or death from MDS</td>
</tr>
<tr>
<td></td>
<td>* DFS: time to relapse</td>
</tr>
<tr>
<td></td>
<td>* Cause-specific death: death related to MDS</td>
</tr>
</tbody>
</table>

### Proposed modified IWG response criteria for haematological improvement

<table>
<thead>
<tr>
<th>Hematological improvement</th>
<th>Response criteria (response must last at least 8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response (pre-treatment&lt;110 g/L)</td>
<td>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</td>
</tr>
<tr>
<td>Platelet response (pre-treatment&lt;100 x10^9/L)</td>
<td>Absolute increase of ≥ 30 x 10^9/L for patients starting with &gt; 20 x 10^9/L. Increase from &lt; 20 x 10^9/L to &gt; 20 x 10^9/L and by at least 100%</td>
</tr>
<tr>
<td>Neutrophil response (pre-treatment&lt;1.0 x10^9/L)</td>
<td>At least 100% increase and an absolute increase &gt; 0.5 x 10^9/L.</td>
</tr>
<tr>
<td>Progression or relapse after HI</td>
<td>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</td>
</tr>
</tbody>
</table>
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. Consider potentially curative treatment (allogeneic stem cell transplantation) for patients with IPSS INT-1, 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 categorised as intermediate risk according to IPSS-R, since few therapeutic studies have so far used this category as a criterion.
2. High-quality transfusion therapy, and chelation therapy, when indicated.
4. For patients with anemia, consider Epo ± G-CSF to patients with predictive score 0 or 1 according to the predictive model.
5. Lenalidomide treatment for patients with IPSS low and INT-1-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. Evaluate patient with hypo-/normocellular bone marrow, normal cytogenetics and a blast count 10-30 % for low dose melphalan, if not eligible for inclusion in available clinical trial.
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.
2. Patients with CMML 2 (10-19 % marrow blasts and promonocytes) and less than 13 x 10⁹/L in leukocytes: Azacitidine.
3. Patients with CMML 2 (10-19% marrow blasts and promonocytes) and more than 13 x \(10^9/L\) in leukocytes: In selected patients, who do not have very elevated leukocyte count, azacitidine treatment can be given (less evidence for its benefit). Alternatively hydroxyurea or AML-like chemotherapy may be given.

4. Patients with CMML 1 (5-9% bone marrow blasts and promonocytes), less than 13 x \(10^9/L\) in leukocytes: and high-risk cytogentics: Treatment with Vidaza should be considered if they are candidates for allogeneic stem cell transplantation. Otherwise: Wait and see. Can be treated with Epo according to recommendations for other low risk MDS.

5. Patients with CMML 1 (5-9% bone marrow blasts and promonocytes) and more than 13 x \(10^9/L\) in leukocytes: Hydroxyurea if symptomatic, Epo if anemia.

Supportive Care

Transfusion

A recent study suggests that quality of life is improved with higher target Hb levels 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 transfusions: Please see thrombocytopenia section.

Iron Chelation

Background

There are currently three different iron chelators available, Desferrioxamin (DFO) to be given preferably by i.v. or s.c. infusion, and Deferasirox 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 with regard to overall survival and morbidity 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 is evidence that all available chelators reduce iron overload in MDS. A large prospective phase 2 trial has been conducted in which 341 patients with MDS were treated with deferasirox 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. 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.

**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**
- Deferasirox should not be given to patients with impaired renal function (elevated creatinine)
- Start with 5-10 mg/kg/day once daily – and increase slowly to a target dose of 20-40mg/kg.
- Deferasirox should be dissolved thoroughly in water or clear liquids to reduce abdominal discomfort.
- Taking the dissolved tablets at mealtime and to divide the daily dose morning and evening, can reduce abdominal discomfort and diarrhea.
- Liver function tests and creatinine should be measured monthly (creatinine weekly for the first month of therapy).
- S-creatinine, S-ALAT and S-ASAT should be measured weekly the first four weeks of treatment. In case of elevated s-creatinine > 2 ULN, deferasirox should be interrupted and then restarted at lower dose.

**Recommendation:**
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 actually considered a good prognostic sign for a response to the treatment. Azacitidine treatment is regularly 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.
Trombopoietin (TPO) receptor agonists romiplostim (Nplate) and eltrombopag (Revolade) are approved for the treatment of immunological trombocytopenic purpura (ITP) but has also been tested in several clinical studies for trombocytopenic 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. The studies are however few with a rather low number of patients and one of the largest studies (240 patients) with romiplostim was terminated earlier owing to the concern of transient increase in peripheral blast cell counts associated with romiplostim treatment. From an efficacy point of view there seems to be less grade 1-2 bleedings and less need for platelet transfusions during treatment with the TPO-agonists but the clinical significans of this is not proven. Thus, so far, romiplostin cannot routinely be recommended for trombocytopenic patients with MDS outside of clinical trials, particularly not to those with more than 5% bone marrow blasts. Data for eltrombopag are even more immature and no recommendation can be given for this drug.

**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. 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. 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 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 $\geq 15$ g/l
- Complete erythroid response (CER)
  - Stable hemoglobin $\geq 115$ 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.

<table>
<thead>
<tr>
<th>Transfusion need</th>
<th>point</th>
<th>S-Epo</th>
<th>Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 units RBC / month</td>
<td>0</td>
<td>&lt;500 U/l</td>
<td>0</td>
</tr>
<tr>
<td>$\geq 2$ units RBC / month</td>
<td>1</td>
<td>$\geq 500$ U/l</td>
<td>1</td>
</tr>
</tbody>
</table>

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 examination 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.

• 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 60 000 U/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 venesection if supranormal Hb levels.

**Darbopoetin 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 150 µg/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 300 µg/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 U 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. Darbopoetin 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, alternatively 120 µg 2-3 times a week.

• 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.

• 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 Ib.

**Recommendation Epo + G-CSF**
Recommendation grade A, evidence level Ib.

**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. An analysis of patients treated at NIH indicated an improvement in survival of ATG treated patients, especially in younger individuals with lower risk disease. Passweg et al. confirmed 29% response in the ATG/Cyclosporin A arm compared to 9% in the supportive care arm, but did not find significant survival improvement. In aplastic anemia, ATGAM™ has been proven superior to other ATG rabbit, but this has not been investigated in MDS. 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 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:**
• There are different ATG products available, and ATG should be used according to local traditions/experience.
  
  o  horse ATG, Genzyme (Lymphoglobuline\textsuperscript{TM}); 15 mg/kg, d 1-5
  o  rabbit ATG, Genzyme (Thymoglobuline\textsuperscript{TM}); 3.75 mg/kg, d 1-5
  o  rabbit ATG, Fresenius (ATG-Fresenius\textsuperscript{TM}); 20 mg/kg, d. 1-3
  o  horse ATG, Pfizer (ATGAM\textsuperscript{TM}); 40 mg/kg, d 1-4

• Prednisolone: 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 a complete stop.
• Prophylaxis with sulfamethoxazol/trimetoprim for 6 months is recommended.
• Consider prophylaxis with fluconazole and acyclovir.

\textbf{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.

\textbf{Recommendation ATG}
Recommendation grade B, evidence level Ib.

\textbf{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)

\textbf{Recommendation CyA}
Recommendation grade B, evidence level III.

\textbf{Lenalidomide}

\textbf{Background}
Lenalidomide is an immunomodulatory drug (IMiD) initially licensed for treatment of multiple myeloma. One small phase II and one large phase III study have shown high response rates in epo-refractory low and INT-1 risk MDS patients with a 5q deletion, which has lead to recent approval for this condition by EMA. In the first study, 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 large randomized phase III 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. As reported in later subset analysis, cytogenetic response rates (major + minor responses) were 56.8% (10 mg group) and 23.1% (5 mg group). Median overall survival in the study was 4.0 yr, 3.5 yr and 2.9 yr in the lenalidomide 10 mg, lenalidomide 5 mg and placebo groups, respectively. For the lenalidomide groups combined, 3-year overall survival and risk of AML were 56.5% and 25.1%, respectively. At 5 years, approximately
35% 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. Saft et al, Haematologica 2013, 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.

**Decision-making and treatment with lenalidomide**

**Treatment with lenalidomide in patients with low and INT-1 risk MDS with isolated del(5q)**
- Treat patients, who are not transplant candidates, with low and INT-1 risk MDS with unmuted TP53 and a karyotype involving isolated del(5q) with lenalidomide when ESAs have failed or are not expected to be effective according to the predictive model for ESA mentioned above. Treat with repeated courses at 10 mg for 21 days with a 7 day break.
- In potential transplant candidates only treat with lenalidomide if the patient is p53 negative by immunohistochemistry. Evaluate regularly for signs of disease progression in case of lack of response to lenalidomide.
- In elderly frail patients and/or patients with renal impairment consider 5 mg days 21/28.
- Prior to lenalidomide treatment, patients should be thoroughly informed about the increased risk of other malignancies, which has been 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 and CMML**

**Background**
Allogeneic stem cell transplantation is the only known curative treatment option in patients with MDS and CMML. Published registry data for MDS show disease free survival rates between 35 and 40%, transplant related mortality (TRM) between 15-25% and relapse rates (RR) 20-30%. Several non-randomised studies have compared reduced intensity conditioning (RIC) transplantation with conventional myeloablative conditioning (MAC) transplantation. 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 %.

Risk factors for TRM are high age, advanced disease stage, therapy related MDS and use of suboptimally matched unrelated donor in addition to the presence of comorbidities. Risk factors for relapse are high age, advanced disease stage, poor risk cytogenetics. In addition, one study found disease duration to be a risk factor for TRM. In most series, patients with advanced MDS had cytoreductive therapy in the form of AML like induction chemotherapy or hypomethylating agents prior to RIC SCT. Randomised prospective studies directly comparing the two strategies have not been done, but several retrospective studies describe no difference in post-transplant outcome. The evidence for debulking in general is rather sparse - at least in slowly progressing diseases. However, 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.

Chronic myelomonocytic leukemia is a challenging disease being difficult to cure even with allogeneic stem cell transplantation. Several prognostic scoring systems have been developed, but the only one that has been validated in a transplant setting is the CPSS developed by Such and colleagues in 2013. The four specific criteria that significantly contribute to OS and the risk for transformation to AML were: WHO subtype, FAB subtype, CMML-specific cytogenetic risk classification and RBC transfusion dependency. For more details regarding CPSS, please see the chronic myelomonocytic leukemia chapter at page 31. The CPSS was validated in 209 transplanted patients by Duong and colleagues in 2015. There was a difference in 5 years 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 int2-/high-risk.

In a large EBMT –study published by Symeonidis and colleagues involving 513 CMML patients the 4-years non-relapse-mortality was 41 % and the RR 32 %. The relapse-free survival was 27 % and OS was 33 %. 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 or hypomethylating agents is recommended from this study.

**Decision making and treatment**

**Indications (sibling or unrelated)**

- Age below 70. Patients older than 70 and in good clinical condition should be considered. The indication should be assessed in association with eventual co-morbid conditions and functional status (see comorbidity index on page 26).
- IPSS INT-1, INT-2, and HR. In INT-1, IPSS-R can help to identify candidates for stem cell transplantation. Poor risk factors (increased blast percentage, cytogenetic and molecular characteristics, cytopenias and transfusion dependence) may be identified in lower risk and intermediate risk patients, indicating a need for an early SCT.
- CMML-2 or CMML-1 with a CPSS with at least int-1 score.
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.

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. Therefore, cytoreductive therapy is usually given before SCT. 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 ≥ 10 % should be considered for cytoreductive therapy.
- Patients with CMML-2 should receive therapy with the aim to obtain the best possible remission before SCT.
- Treatment should be determined in close collaboration with the local transplant team and usually involves azacitidine or AML like chemotherapy.

Decision making

- At diagnosis 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) are 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/). 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>
<thead>
<tr>
<th>Comorbidity</th>
<th>Definition of comorbidity</th>
<th>HCT-CI weighted score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Coronary artery disease, ≥ congestive heart failure, myocardial infarction, or EF ≤ 50%</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Crohn disease or ulcerative colitis</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Requiring treatment with insulin or oral hypoglycemics but not diet alone</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Transient ischemic attack or cerebrovascular accident</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>Depression or anxiety requiring psychiatric consult or treatment</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic, mild</td>
<td>Chronic hepatitis, bilirubin &gt; ULN to 1.5 x ULN, or AST/ALT &gt; ULN to 2.5 x ULN</td>
<td>1</td>
</tr>
<tr>
<td>Obesity</td>
<td>Patients with a body mass index &gt; 35 kg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>Requiring continuation of antimicrobial treatment after day 0</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica</td>
<td>2</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Requiring treatment</td>
<td>2</td>
</tr>
<tr>
<td>Moderate/severe renal</td>
<td>Serum creatinine &gt; 2 mg/dL (178 mmol/l), on dialysis, or prior renal transplantation</td>
<td>2</td>
</tr>
<tr>
<td>Moderate pulmonary</td>
<td>DLco and/or FEV₁ 66%-80% or dyspnea on slight activity</td>
<td>2</td>
</tr>
<tr>
<td>Prior solid tumour</td>
<td>Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer</td>
<td>3</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>Except mitral valve prolapse</td>
<td>3</td>
</tr>
<tr>
<td>Severe pulmonary</td>
<td>DLco and/or FEV₁≤ 65% or dyspnea at rest or requiring oxygen</td>
<td>3</td>
</tr>
<tr>
<td>Moderate/severe hepatic</td>
<td>Liver cirrhosis, bilirubin &gt; 1.5 x ULN, or AST/ALT &gt; 2.5 x ULN</td>
<td>3</td>
</tr>
</tbody>
</table>

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 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 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). 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 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.
- Significant cytopenia (if not, follow up frequently).
- Expected survival exceeding 3 months.

Treatment Azacitidine
- Azacitidine 75 mg/m² sc d 1-7 repeated every 28 days. (alternative dosing schedules can be considered: 100 mg/m² sc d 1-5 or 75 mg/m² sc d 5-2-2).
- 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 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, 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. Many 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. 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), IPSS-R intermediate and MDS-AML
• Remission induction of younger patients prior to allogeneic SCT.
• In patients not eligible for allogeneic SCT if
  o good prognostic features for CR, ie normal s-LDH and/or WBC <4.0 x10^9/L, good or intermediate risk cytogenetics.
  o 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**

**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.

- **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 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 azacitidine.

- 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/m²/day sc, for 2-8 weeks. Maintenance treatment might be given to responders.

**Recommendation**
Recommendation grade A, evidence level Ib.

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**Chronic myelomonocytic leukaemia**

**Background**
Chronic myelomonocytic leukaemia is a rare disease with an incidence of 3/100,000/year in a 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 $>13 \times 10^9/L$, and a dysplastic form (CMML-MD) with white cell counts below $13 \times 10^9/L$.

**Diagnostic criteria (according to WHO 2008):**

1. A persistent monocytosis of $>1 \times 10^9/L$ 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 PDGFR\textsubscript{A} or PDGFR\textsubscript{B} genes.
4. No more than 19 \% blasts, and this includes myeloblasts and promonocytes.
5. Dysplasia in one or more lineages (not needed in case of monocytosis $>3$ months provided other causes are excluded or clonal proof).

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. SRSF2 mutations are seen in 40-45 \% and ASXL1 mutations in 50 \% of the patients and both mutations seem to confer a worse prognosis. The WHO 2008 classification divides CMML into two groups based on the number of blasts: CMML-1: $<10 \%$ medullary blasts (including promonocytes) and $<5 \%$ peripheral blasts (including promonocytes), CMML-2: 10-19 \% blasts (including promonocytes) and/or 5-19 \% peripheral blasts (including promonocytes), 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 $>12 \times 10^9 /L$. 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 (\geq 3) abnormalities, and prior transfusions.

CMML specific scoring system (CPSS, Such et al) 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 OS for low, intermediate-1, intermediate-2 and high risk were: 61, 31, 15 and 9 months.

### Score values

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts (%)</td>
<td>Points</td>
</tr>
<tr>
<td>&lt;10 % in BM and &lt; 5 % in PB</td>
<td>0</td>
</tr>
<tr>
<td>10-19 % in BM or 5-19 % in PB</td>
<td>1</td>
</tr>
<tr>
<td>White cell count</td>
<td>Points</td>
</tr>
<tr>
<td>Up to $13 \times 10^9/L$</td>
<td>0</td>
</tr>
<tr>
<td>$&gt;13 \times 10^9/L$</td>
<td>1</td>
</tr>
<tr>
<td>Karyotype\textsuperscript{°}</td>
<td>Points</td>
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<tr>
<td>Low risk</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
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</tr>
<tr>
<td>High risk</td>
<td>2</td>
</tr>
<tr>
<td>Transfusion dependency</td>
<td>Points</td>
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<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: BM = bone marrow. PB = peripheral blood. \textsuperscript{°} Low risk: normal, -Y, del(5q), del(20q). High risk: trisomy 8, complex (\geq 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities.

**Decision-making and treatment**

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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**

See page 24 for general recommendations regarding allogeneic stem cell transplantation in MDS and CMML.

**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.

**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 x 10^9/l).

One retrospective single center study investigated effects of azacitidine in CMML with leukocyte counts below and above 13 x 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. 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-azacitidine and decitabine. For CMML patients with less than 13 x 10^9/L leukocytes, with an increase of blasts and for whom there is an aim to prolong survival, 5-azacitidine is recommended as 1st line treatment. Treatment should be planned to be given for at least 6 cycles. For CMML patients with leukocytes
above 13 x 10^9/L, there is less evidence supporting azacitidine treatment. The higher the leukocyte count the less likely is the patient to respond.

**Recommendation:**
Recommendation grade A, evidence level 1b.

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**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. Azacitidine 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.

**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**
- 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), especially in case of intolerance to azacitidine.
- Not candidates for curative treatment or induction chemotherapy.

**Treatment Decitabine**
- Decitabine 15 mg/m² by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks. Alternatively 20 mg/m², 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 haematological improvement.

**Recommendation**
**Decitabine:** 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

**Disclosure statement**
AOK: Covered congress/travel expences by Celgene
LC: None
ID: Covered congress/travel expences by Celgene
FE: Expert statement for Celgene, congress/travel expenses covered by Amgen and Novartis
LF: None
HG: None
EHL: Research grant for clinical trials Celgene
MH: None
KRJ: Covered congress/travel expences - Celgene and Novartis, Advisory board - Novartis Honorarium for lectures/meeting chairman - Celgene
MJ: Honorarium for lectures from Celgene and Novartis
LK: None
FL: None
PL: None
LN: Honorarium for lectures from Celgene
JN: None
LS: None

References

Diagnosis and supportive care


Leitch HA. Improving clinical outcome in patients with myelodysplastic syndrome and iron overload using iron chelation therapy. Leuk Res. 2007 Dec;31.


Epo+G-CSF treatment


ATG+CyA


**Lenalidomide**


Allogeneic transplantation


Martino R, de Wreede L, Fiocco M et al. Comparison of conditioning regimens of various intensities for allogeneic hematopoietic SCT using HLA-identical sibling donors in AML and MDS with <10 % BM blasts: a report from EBMT. Bone Marrow Transplant 2013; 48: 761-770.


Azacitidine


**AML like chemotherapy**


**Low dose chemotherapy**


MDS Guideline Programme


Chronic myelomonocytic leukemia


Emanuel PD: Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. Lekmia (2008)22;1335-1342


Treatment alternatives which are not commercially available or of uncertain usefulness


