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

Nordic MDS Group

Issue 5

4th update, January 2010
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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, which will be published on-line at the website www.nordicmds.org. The Guidelines are written for health professionals with a speciality or an interest in hematology. It will be updated at least yearly, 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.nordicmds.org in November 2004. The present version, issue #5, constitutes the fourth update.


Writing committee

Lars Kjeldsen (chair), Ingunn Dybedal, Robert Hast, Eeva Juvonen, Anna Olsson, Sigrun Reykdal, and Eva Hellström Lindberg. From 2008, Robert Hast and Anna Olsson have been replaced by Mette Skov Holm, Lars Nilsson and Hege Garelius.

Contact information

The email addresses of the writing committee are found at www.nordicmds.org. Comments to the group could be directed to nmds@medhs.ki.se, or directly to one of the committee members.
News in issue 4

An algorithm for treatment of CMML (page 15) and a paragraph describing the treatment of CMML (page 33) are included.

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>IIa</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. The diagnostic criteria should distinguish MDS from reactive causes of cytopenia and dysplasia as well as from other clonal stem cell disorders.

Diagnostic work-up of MDS:

**Patient history and examination:**
This should include family history, prior chemotherapy and irradiation, occupational exposure, concomitant medication, tendency for bleeding/bruising and infection, and a complete physical examination including spleen size.

**Blood tests:**
- WBC, differential, hemoglobin, platelet count, red blood cell indices (MCV, MCHC, RDW) and reticulocyte count. For dysplasia, see below under bone marrow evaluation.
- Homocysteine, if elevated ≥ 25-30 µmol/L and normal renal function: measure RBC-folate/S-folic acid, and serum cobalamins. Hematologically significant cobalamin/folate deficiency usually causes homocysteine > 30 (twice the upper reference limit). In such cases, response to adequate vitamin therapy is: falling transferrin saturation within 24h, increased reticulocytes d5-6, increasing Hb, decreasing MCV in 2-3 weeks.
- Iron, transferrin (TIBC), ferritin, LDH, bilirubin, haptoglobin, DAT (Coombs test), ALAT, ASAT, Alkaline phosphatase, albumin, uric acid, creatinine, S-erythropoietin, S-protein electrophoresis (S-immunoglobulins).
- Screening for HIV, Parvovirus B19 (hypoplastic MDS). Screening for hepatitis B and C in transfusion dependent patients.

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

- Bone marrow aspirate and biopsy.
  For significant dysplasia, dysplastic features should be present in at least 10% of the nucleated cells in the lineage in consideration. At least 200 marrow cells and 20 megakaryocytes should be evaluated and an optimal staining of blood and marrow slides is important. The presence of pseudo-pelger neutrophils, ring sideroblasts, micromegakaryocytes and increased blast count show the strongest correlation with clonal markers in MDS.

- A cytogenetic analysis should be done in all cases.
- A flow cytometric analysis (CD34+ cell count) is relevant in high-risk disease.

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

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


## Classifications

The Nordic MDS group recommends classification according to WHO only, where a revised 2008 classification has been published just recently. For historical reasons and since some may still classify according to FAB, the FAB classification is still included below.

### WHO 2008 classification of MDS

#### Peripheral blood and bone marrow findings in myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenias with unilineage dysplasia (RCUD)</td>
<td>Unicytopenia or bicytopenia&lt;sup&gt;1&lt;/sup&gt;</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>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>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%)&lt;sup&gt;2&lt;/sup&gt;</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;1x10&lt;sup&gt;9&lt;/sup&gt;/l monocytes</td>
<td>±15% ring sideroblasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>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% blasts&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt;1x10&lt;sup&gt;9&lt;/sup&gt;/l monocytes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>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>No Auer rods</td>
<td>Auer rods:</td>
</tr>
<tr>
<td></td>
<td>&lt;1x10&lt;sup&gt;9&lt;/sup&gt;/l monocytes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>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% blasts&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5% blasts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>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>

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<sup>1</sup> Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

<sup>2</sup> 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.

<sup>3</sup> Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2
WHO classification 2008 of myelodysplastic/myeloproliferative neoplasms

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelomonocytic leukaemia (CMML)</td>
<td>Peripheral blood monocytosis &gt; 1x10⁹/l</td>
<td>Dysplasia in one or more myeloid lineage¹ &lt;20% blasts. Blasts include myeloblasts, monoblasts and promonocytes. No rearrangement of PDGFRA or PDGFRB</td>
</tr>
<tr>
<td></td>
<td>No BCR/ABL-1 fusion gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;20% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)</td>
<td>Leukocytosis, neutrophilia</td>
<td>Neutrophil dysplasia with or without dysplastic lineages &lt;20% blasts</td>
</tr>
<tr>
<td></td>
<td>Neutrophilic dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophil precursors ≥10% of leukocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blasts &lt;20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No BCR-ABL1 fusion gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No rearrangement of PDGFRA or PDGFRB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal basophilia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytes &lt; 10% of leukocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukaemia (JMML)</td>
<td>Peripheral blood monocytosis &gt;1x10⁹/l</td>
<td>&lt;20% blasts. Evidence of clonality</td>
</tr>
<tr>
<td></td>
<td>&lt;20% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually WBC &gt; 10x10⁹/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)</td>
<td>Mixed MDS and MPN features</td>
<td>Mixed MDS and MPN features</td>
</tr>
<tr>
<td></td>
<td>No prior diagnosis of MDS or MPN</td>
<td>&lt;20% blasts</td>
</tr>
<tr>
<td></td>
<td>No history of recent growth factor or cytotoxic therapy to explain MDS or MPN features</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No BCR-ABL1 fusion gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No rearrangements of PDGFRA or PDGFRB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹Refractory anaemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) (provisional entity)²</td>
<td>Persistent thrombocytosis &gt;450x10⁹/l</td>
<td>Morphologic features of RARS; ≥ 15% of erythroid precursors are ring sideroblast Abnormal megakaryocytes similar to those observed in BCR-ABL1 negative MPN</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BCR-ABL1 negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cases with t(3;3)(q21;q26), inv(#)(q21q26) and isolated del(5q) are excluded</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>²If myelodysplasia minimal or absent, CML can still be diagnosed if the other requirements are met and there is an acquired clonal cytogenetic or molecular genetic abnormality. Biclonality may occasionally be observed. Cases with pancytopenia should be classified as MDS-U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>²If the marrow myeloblast percentage is &lt;5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is &lt;5% and there are 1% myeloblasts in the blood, the case should be classified as MDS-U.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>²Cases with Auer rods and &lt;5% myeloblasts in the blood and &lt;10% in the marrow should be classified as RAEB-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FAB-classification of MDS  
(Bennett et al, 1982)

It is no longer recommended to use the FAB classification for newly diagnosed patients. The FAB classification remains in the guidelines mainly for patients who were diagnosed prior to implementation of the WHO 2001 classification.

<table>
<thead>
<tr>
<th>Type</th>
<th>Blasts in BM</th>
<th>Blasts in blood</th>
<th>Siderobl. in BM</th>
<th>Monocytes in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>&lt;5%</td>
<td>&lt;1%</td>
<td>- (&lt;15%)</td>
<td>&lt;1 x 10^9/l</td>
</tr>
<tr>
<td>RARS</td>
<td>&lt;5%</td>
<td>&lt;1%</td>
<td>+ (&gt;15%)</td>
<td>&lt;1 x 10^9/l</td>
</tr>
<tr>
<td>RAEB</td>
<td>5-20%</td>
<td>&lt;5%</td>
<td>+ / -</td>
<td>&lt;1 x 10^9/l</td>
</tr>
<tr>
<td>CMML</td>
<td>5-20%</td>
<td>&lt;5%</td>
<td>-</td>
<td>&gt;1 x 10^9/l</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>21-29%</td>
<td>&lt;30%</td>
<td>+ / -</td>
<td>&lt;1 x 10^9/l</td>
</tr>
</tbody>
</table>

AML ≥30% ≥30% + / -

AML after a well established phase of MDS is classified as MDS-AML
Prognosis

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.

<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>

Score value

<table>
<thead>
<tr>
<th>Prognostic variable</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>-</td>
<td>11-20</td>
<td>21-30</td>
</tr>
<tr>
<td>Karyotype°</td>
<td>Good</td>
<td>Intermed.</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias*</td>
<td>0/1</td>
<td>2/3</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 10^9/l, platelets <100 x 10^9/l.

Low risk vs High risk MDS

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

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

<table>
<thead>
<tr>
<th>WPSS risk group</th>
<th>Score</th>
<th>Median survival Italian cohort (months)</th>
<th>Median survival German cohort (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
<td>103</td>
<td>141</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Very high</td>
<td>5-6</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td>RA, RARS, isolated 5q-</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Transfusion requirement†</td>
<td>No</td>
<td>Regular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Good: normal, −Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; and intermediate: other abnormalities.
†At least 1 RBC transfusion every 8 weeks over a period of 4 months.

Recommendation for diagnosis and prognosis

- All patients should be classified according to WHO 2008 classification.
- All patients should be risk stratified according to IPSS.
- 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>
</table>
| Complete remission        | Bone marrow ≤ 5% myeloblasts with normal maturation of all cell lines  
                           | Persistent dysplasia will be noted  
                           | Peripheral blood:  
                              | Hb ≥ 110 g/l,  
                              | Platelets ≥ 100 x10^9/L,  
                              | Neutrophils ≥ 1.0 x10^9/L  
                              | Blasts 0% |
| Partial remission         | All CR criteria if abnormal before treatment except:  
                           | Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5%  
                           | Cellularity and morphology not relevant |
| Marrow CR                 | BM ≤5% myeloblasts and decrease by ≥ 50% over pre-treatment  
                           | Peripheral blood: if HI responses, they will be noted in addition to marrow CR |
| Stable disease            | Failure to achieve at least PR, but no evidence of progression for > 8 wks |
| Failure                   | Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of BM blasts, or progression to a more advanced MDS subtype than pretreatment |
| Relapse after CR or PR    | At least one of the following:  
                           | Return to pretreatment BM blast percentage  
                           | Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets  
                           | Reduction in Hb concentration by ≥ 15 g/L or transfusion dependence |
| Cytogenetic response      | Complete: Disappearance of the chromosomal abnormality without new ones  
                           | Partial: At least 50% reduction of the chromosomal abnormality |
| Disease progression       | ≥ 50% increase in blasts  
                           | Any of the following:  
                              | At least 50% decrement from maximum remission/response in granulocytes or platelets  
                              | Reduction of Hb by ≥ 20g/L  
                              | Transfusion dependence |
| Survival                  | Endpoints:  
                           | Overall: death from any cause  
                           | Event free: failure or death from any cause  
                           | PFS: disease progression or death from MDS  
                           | DFS: time to relapse  
                           | Cause-specific death: death related to MDS |

### Proposed modified IWG response criteria for haematological improvement

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

We recommend that all newly diagnosed patients are evaluated at a center with hematological experience. Patients should undergo regular follow-up including blood tests. If a patient is considered to be a candidate for therapeutic intervention at disease progression, regular bone marrow analysis is recommended.

Due to the vast heterogeneity of the disease, therapeutic options range from observation only to allogeneic SCT. Decision-making about treatment may be difficult. It is essential that patients are evaluated for curative approaches at diagnosis, since e.g. allo-SCT in progressive phase of MDS has a poor outcome. It is our recommendation that suitable patients are offered treatment within study protocols or, alternatively, are treated according to the recommendations of the Nordic MDS-group.

Algorithm for treatment of symptomatic low-risk MDS

1. High-quality transfusion and chelation therapy.
2. Evaluate patients with IPSS INT-1 for curative treatment (allogeneic stem cell transplantation).
4. For patients with anemia, consider Epo ± G-CSF to patients with predictive score 0 or 1 according to the predictive model.
5. Patients with severe cytopenia and/or transfusion dependency who have failed other relevant therapies may be considered for azacitidine treatment, preferably within a clinical trial
6. Predictive group 3 or patients who do not respond to Epo + G-ÇSF should be given only transfusion therapy, or experimental treatment within protocols.
7. Regarding lenalidomide treatment, this should be used with extreme precaution and not without discussion with a member of NMDS. Patients treated must be reported to the NMDSG registry, www.nordicmds.org. See specific chapter on page 30 for details

Algorithm for treatment of patients with high-risk MDS

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

Algorithm for treatment of patients with CMML

1. Evaluate for curative treatment, allogeneic stem cell transplantation.
2. Evaluate patient for azacitidine treatment; CMML with an increase of blasts and for which there is an aim to prolong survival
3. Evaluate patient for hydroxyurea treatment; symptomatic elderly patients with a low (<10%) marrow blast count and for which the main aim is to reduce symptoms.
4. Supportive care only or experimental treatment within a protocol.
Supportive Care

Transfusion

Published data are limited in MDS, general criteria are based on clinical experience. *Use leukocyte-filtered blood products.*

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

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

Iron Chelation

Desferrioxamine (DFO)

**Background:**
Limited data are available on 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 strong evidence that iron chelation with DFO reduces iron overload in MDS. However, there are no studies proving the effect of iron chelation on long-term outcome in MDS. The goal of the treatment is to achieve a safe tissue iron concentration by promoting negative iron balance and iron detoxification. It has been reported that tissue injury can be halted in spite of very high tissue iron levels using continuous infusion of Desferrioxamine.

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

**DFO treatment**
- 40 mg/kg (20-50 mg) by subcutaneous infusion over 8-12 hours 5-7 days pr week.
• Alternatively give DFO 6-10 g via HomePump over 4-5 days from beginning of each transfusion (especially if the patient has Port-a-Cath).
• Continuous (uninterrupted) 24 hour DFO should be considered in patients at high risk, e.g. with Ferritin persistently >2500 µg/l and significant cardiac disease.

Monitoring DFO:
• The target Ferritin level is <1000 µg/l.
• In case of rapidly decreasing ferritin to less than 1500µg/l, DFO dose should be reduced and not exceed 25 mg/kg.
• Vitamin C 2-3mg/kg/d should be started 4 weeks after the onset of DFO therapy to improve iron excretion.
• Audiometry and Ophthalmology evaluation prior to starting DFO and yearly.

Recommendation:
Recommendation grade B, evidence level III.

Oral chelators:

Deferasirox

Background:
Deferasirox belongs to a new class of iron chelators. Efficient mobilization of tissue iron has been demonstrated in thalassemia but there are no controlled data in MDS. Iron excretion occurs almost entirely in the faeces and is dose dependent. In studies on thalassemia patients side effects are generally mild and include transient gastrointestinal events, skin rash, mild increase in serum creatinin and increased transaminases. There are reports on patients with a rapid renal failure due to deferasirox treatment.

Indication
• Use for adult patients with se-Ferritin >1500 µg/l or after approximately 25 units red cell transfusions, in case of intolerance to DFO or when DFO is inadequate. Use according to local guidelines.
• For WHO RA, RARS and 5q- patients iron chelation is indicated, unless very high age, or severe concomitant disease
• In RCMD and more advanced MDS, iron chelation should only be considered for patients with a life expectancy exceeding 2 years
• In candidates for allogeneic transplantation iron overload should be avoided, special consideration for iron chelation important
• Estimated creatinine clearance should be above 60 ml/min.

Treatment
• 10-30 mg/kg/day once daily – consider slow dose increase

Monitoring
• Monitoring as with DFO. In addition liver function tests and creatinine should be measured monthly (creatinine weekly for the first month of therapy).
Recommendation:
Recommendation grade B, evidence level III

Deferiprone (L1)

Background:
There are very few studies on the use of L1 in MDS. The reported efficacy varies. A higher urinary excretion was reported in thalassemia than in MDS, negative iron balance was achieved in 56% in one study. Rate of agranulocytosis is less than initially reported, < 1%.
Please note that L1 is not available in all Nordic countries.

Indication:
- Use for adult patients with se-Ferritin >1500 µg/l or after approximately 25 units red cell transfusions, in case of intolerance to DFO or when DFO is inadequate. Use according to local guidelines.
- For WHO RA, RARS and 5q- patients iron chelation is indicated, unless very high age, or severe concomitant disease
- In RCMD and more advanced MDS, iron chelation should only be considered for patients with a life expectancy exceeding 2 years
- In candidates for allogeneic transplantation iron overload should be avoided, special consideration for iron chelation important

Treatment:
- 75 mg/kg in three divided doses

Monitoring:
- Monitoring as with DFO. In addition, check blood counts weekly to rule out deferiprone-induced neutropenia.

Recommendation:
Recommendation grade B, evidence level III.

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

Treatment and prevention of infections

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

G-CSF treatment: Can be considered as prophylaxis for severely neutropenic patients with recurring, serious infections or during infectious episodes. Published data are limited.
Treatment of low-risk MDS not eligible for curative approaches

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

Background
Treatment with erythropoietin (Epo) may improve hemoglobin levels and alleviate transfusion need in MDS patients with anemia. The effect of Epo may be enhanced by G-CSF, which synergises with Epo to improve survival and proliferation of early erythroblasts. There is one randomised controlled phase III study on Epo alone vs placebo, and one randomised open phase III study on Epo + G-CSF vs supportive care, both showing a significant effect on hemoglobin levels. There is one randomised phase II trial showing better efficacy of the combination compared to Epo alone. In addition, a large number of phase II trials, of which some are randomised, support the use of this treatment. Patients should be evaluated according to the predictive model for a response to Epo + G-CSF before a decision about treatment.

Darbepoetin (DA) has been evaluated in some small and one larger phase II trial. The efficacy is at least comparable to Epo, but modes of dosing are less well described than for Epo.

NMDSG recently published a retrospective well controlled epidemiological study suggesting a positive effect of treatment with Epo+G-CSF on survival in patients with a transfusion need <2U/month, with no effect on leukemic transformation

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 recent 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

<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 should be treated with the combination from the beginning and for 16 weeks.
- If no response (at least PER) after 16 weeks, treatment is terminated. This should be clarified to the patient prior to treatment initiation.
- If patients on Epo monotherapy loose their response, the Epo dose could be increased or G-CSF can be added. Evaluate after a maximum of 16 weeks.
- Check S-ferritin regularly. If the ferritine value drops below the upper limit of the normal range, start oral or iv iron treatment
- Bone marrow sampling at least once yearly while on treatment or in any case of lost response is generally recommended.

Epo dosing

- Target hemoglobin level <120 g/l
- **Induction phase.** In general, start with maximum dose of Epo 60 000 U/week. The majority of scientific evidence is based on three divided doses / week, but a few recent studies has used two or even one weekly dose with similar effects. Since there is no controlled studies comparing dose intervals, we recommend that patients are started on three weekly doses.
- The starting dose in low weight patients with stable anemia, and always in case of reduced renal function should be lower: 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 lower doses. These doses cannot be recommended
- **Maintenance phase.** In case of CER with Hb>120 g/l, decrease the weekly dose every 8 weeks. Recommended schedule: 60-40-30-20-15-10-5 000 / week) Usually injection days are reduced to 2 - 1, while dose / injection is maintained. Median maintenance dose is 30 000 U (range 5-60 000), somewhat higher for RARS than RA.
- **Overdose.** If Hb above upper normal range, interrupt Epo treatment and restart at 50% of dose when Hb decreases below approximately 120 g/l. Consider venesectio if supranormal Hb levels

Darbepoetin dosing

There is yet limited scientific data on DA dosing in MDS, while these recommendations are based on a few phase II studies, and on personal experience within NMDSG. There are a few reports on thromboembolic disease in DA treated MDS patients. A starting dose of 300 µg/week (suggested to be equal to 60 000 Epo) is therefore not recommended.

- Target hemoglobin level <120 g/l
• **Induction phase.** In general, start with 300 µg / 14 days or 150µg /week. Maximum dose in case of no response 300 µg / week.
• The starting dose in low weight patients with stable anemia, and always in case of reduced renal function should be lower, 150 µg / 14 days.
• **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.** As for Epo

**G-CSF dosing**
• Start with 300 µg / week, sc, in three divided doses. Patients should save the vial in the refrigerator and take out 100 µg / injection day.
• Treatment should aim at a clear rise in neutrophil count, in previous studies 6-10 x 10⁹/l. If no response, increase the dose to a maximum of 300 µg x 3 / week.
• In case of high neutrophil counts, reduce to 2 – 1 injections / week, then reduce dose / injection.
• There is clinical experience that it is effective to dose twice weekly during maintenance phase

**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.
• If no response to increased dosing, consider Azacitidine

**Recommendation Epo**
Recommendation grade A, evidence level 1B.

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

**Recommendation DA±G-CSF**
Recommendation grade B, evidence level IIB

**Immunosuppressive treatment**

**Background**
A small fraction of low risk MDS patients with RA and RCMD seem to have bone marrow failure due to autoimmune mechanisms, as known from aplastic anemia. Several international studies have demonstrated response rates in the order of 30% to immunosuppressive therapy (antithymocyte globulin [ATG] in some investigations combined with cyclosporin A [CyA]) in patients with RA and RCMD. HLA-DR15 positivity, young age and short duration of red cell transfusion dependence seem to predict for a response to immunosuppressive therapy in MDS patients, although this is based on a limited material. A recent analysis of patients treated at NIH indicated an improvement of survival of ATG treated patients, especially in younger individuals with lower risk disease.
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 in a recent retrospective analysis.

**Decision-making and treatment with ATG**

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

**Positive criteria**
- Age: <70 years
- IPSS LR or INT-1

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

**Treatment:** Follow local guidelines for ATG treatment
- There are different ATG products available, and ATG should be used according to local traditions/experience.
  - horse ATG [ATGAM], Pfizer; 40 mg/kg, d 1-4
  - horse ATG, Genzyme; 15 mg/kg, d 1-5
  - rabbit ATG, Genzyme; 3.75 mg/kg d. 1-5
  - rabbit ATG, Fresenius; 20 mg/kg, d. 1-3

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

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

**Recommendation ATG**
Recommendation grade B, evidence level IIa.

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

Conventional allogeneic SCT

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

Decision making and treatment
Indications (sibling or unrelated)
- Age below 55-60.
- IPSS INT-1, INT-2 and HR
- Performance status 0, 1 or 2
- No serious co-morbid conditions (renal disease, heart diseases)

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

Decision making
- At diagnosis consider if the patient is a candidate for allogeneic stem cell transplantation (myeloablative or reduced intensity conditioning). It is not recommended to wait for significant disease progression before a decision about allogeneic transplantation is taken.
- Prior to decision-making regarding allogeneic transplantation, the patient should be thoroughly informed by his/her physician about benefits and risks with transplantation. Any patient must be individually evaluated and should be discussed by the care taking physician and the transplant unit.
- Evaluate patient for potential comorbidities (according to Sorror, Blood 2005).
- In case of IPSS INT-1, consider immunosuppressive treatment and/or Epo+G-CSF, before proceeding to transplantation.
- The decision to proceed to transplantation should be taken by the patient in collaboration with his/her physician and the transplant unit.
- In case decision to transplant – proceed immediately with HLA typing and family work-up.
- If no sibling available, search for unrelated donor.
- All transplant related procedures (conditioning, immunosuppression and supportive care) are performed according to local guidelines.

Cytoreductive chemotherapy prior to myeloablative SCT in patients with high risk MDS (>10% blasts) and MDS/AML
- The value is not established due to lack of randomised trials and conclusive retrospective data. The relapse risk after allo SCT is significantly higher for patients with high blast counts than for patients with CR after induction chemotherapy. On the other hand, induction chemotherapy may in some patients give rise to severe side effects, which prevents SCT.
- Treatment should be determined in close collaboration with the local transplant team and usually involves AML like chemotherapy. If this fails, or if very poor predictive variables;
hypercomplex karyotype, severe fibrosis, severe infection upfront azacitidine can be
considered.

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

## Reduced intensity conditioning (RIC) SCT

### Background
Published series of RIC SCT are still limited, with low number of patients and follow-up not exceeding 3 years. Furthermore, conditioning regimens and immunosuppressive therapy differ considerably. From the publications, it appears that RIC SCT is feasible and potentially curative even in elderly patients (up to the age of 70 years) with comorbidities precluding ablative SCT. Overall survival average 40%, ranging from 27 to 60%. Relapse rates range from 25 to 47% with TRM from 15 to 41%. In most series, patients with advanced MDS had remission inducing AML like chemotherapy prior to RIC SCT. Patients, who did not obtain a reduction of blast count pretransplant to below 5%, were at high risk for relapse. Due to the short follow-up and limited number of patients transplanted, reduced intensity transplantation still has to be regarded as experimental therapy.

### Decision making and treatment

#### Indications (sibling or unrelated)
- Age up to 70 years or below 55-60 with co-morbid conditions preventing conventional conditioning
- IPSS INT-1, INT-2 and HR
- Performance status 0, 1 or 2
- No serious co-morbid conditions (renal disease, heart diseases, liver disease)
- In case of advanced MDS, AML like chemotherapy or azacitidine should be given to obtain a reduction of blast count to below 5% pretransplant
- If no contraindications against ablative SCT, RIC SCT should only be performed within a clinical trial

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

#### Recommendation
- Recommendation grade B, evidence level III
Treatment of high-risk MDS and MDS/AML in patients not eligible for allogeneic stem cell transplantation

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

Azacytidine

Background
Azacitidine is approved by both FDA and EMEA 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 recent randomised phase III study of patients with advanced MDS not primarily eligible for curative treatment (SCT), compared azacitidine to best standard of care (BSC), where the treating physician could choose between best supportive care only, best supportive care with low dose cytarabine or best supportive care with AML-like chemotherapy. The study demonstrated a significant improvement in overall survival with azacitidine (24 vs 15 months, p=0.0001) and time to AML transformation (24 vs 12 months, p=0.004). Twenty-nine % of azacitidine treated patients responded with CR or PR.

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.

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
- Not candidates for curative treatment
- 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 used if requested by patients eg 100 mg/m² sc d 1-5)
- Continue treatment unless obvious signs of progression. Responses are rare after 1 to 2 courses of treatment
- Evaluate response (bone marrow assessment) after 4-6 courses unless there is overt progression or indications of overdosing earlier.
- In case of response, recovery of peripheral blood values may be delayed due to suppressive effects of azacytidine. It may be useful to make an 8 weeks pause after cycle 6 to see if recovery occurs.
- It is not totally clear how to proceed in case of a very good response after 6-8 cycles. The MDS 001 trial recommends continuous treatment with unchanged dose. However, many patients will not tolerate this treatment, and in elderly/fragile patients it may be a good choice to stop treatment and continue in case of progression. It is at the moment difficult to make specific recommendations and we recommend discussion with regional/national coordinators.
- Specific guidelines including instructions to nurses may be obtained from the Nordic MDS group coordinators.

Recommendation

Recommendation grade A, evidence level 1b.

AML like chemotherapy

Background

A number of studies have been published where a total of more than 1100 patients with HR-MDS or MDS-AML have been treated with different combinations of induction chemotherapy. Only few studies were randomized, and then often with the purpose to study the effect of G-CSF or GM-CSF in combination with chemotherapy. All studies taken together showed a median complete remission (CR) rate of 43% (range: 18-74%), and overall survival (OS) varying between 6-21 months. Between 8-27% of the patients died within the first month of treatment. Patients with normal LDH and/or WBC <4x10⁹/l and absence of poor risk cytogenetics had better CR rates. In some studies, duration of antecedent MDS was inversely related to achievement of CR. CR durations are generally short and there is no evidence, that AML like chemotherapy alters the natural history of MDS, ie overall survival is not affected by the treatment. There are no data to support that high dose chemotherapy with autologous stem cell support is superior to AML like chemotherapy. Hence, no recommendation can be made as to the preferred use of autologous stem cell transplantation in younger HR-MDS and MDS-AML patients.
Decision making and treatment

Indication for AML like chemotherapy
Consider younger patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML
- not eligible for allogeneic SCT
- good prognostic features for CR, ie normal s-LDH and/or WBC <4.0 x10^9/L, good or intermediate risk cytogenetics
- deemed to tolerate induction chemotherapy.

In elderly patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML (less than 30% blasts),
- azacitidine is recommended as first choice.
- in elderly, where azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR

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

- Younger patients are treated with standard AML induction chemotherapy according to local protocols.
- Elderly patients are treated with standard AML-like induction chemotherapy of intermediate dose intensity, like DA(2+7) or DA(3+7) [daunorubicin 60 mg/m^2 days 1+2 or days 1-3 and cytosine arabinoside 100 mg/m^2 x2 i.v. or s.c. days 1-7].
- 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.
- When consolidation therapy is indicated in CR, the dose intensity and number of courses should take into account the clinical status of the patient, and the toxicity of prior courses.
- Resistant disease and relapse treatment according to local protocols or recommendations.
- 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)

Recommendation Growth factors
- Recommendation grade A, evidence level Ia.

Low dose chemotherapy

General background
There is insufficient evidence to recommend routine use of low-dose chemotherapy, since there are no data showing a beneficial effect on survival or transformation to AML in unselected groups of patients. However, in individual patients low-dose chemotherapy may be used to reduce high white blood cell counts as well as bone-marrow blast counts, and to improve pancytopenia in MDS.
Melphalan
Three small phase 2 studies in high-risk MDS patients report a response rate of up to 30% in selected patients, i.e. improved blood cell counts and reduced/abolished transfusion need. The toxicity was mild.
- Suggested indication: Symptomatic high risk MDS and MDS/AML patients with a normal karyotype and a hypo/normocellular bone marrow.
- Dosage: 2 mg/day until response (usually 8 weeks) or progression.

Recommendation grade B, evidence level IIb.

Low-dose cytosine arabinoside

One large randomised study comparing low dose cytosine arabinoside (LDAC) and supportive care in predominantly high-risk MDS patients showed a response rate of approximately 30% in the LDAC arm, but no benefit in terms of overall survival and transformation to AML. Fatal hematological toxicity at a frequency of up to 19% was reported for LDAC.
- 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 grade A, evidence level Ib

Treatment alternatives which are not commercially available or of uncertain usefulness

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

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

Decitabine

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

A large phase II study showed that Decitabine had significant effects also in high-risk MDS, and that major cytogenetic responses could be observed in 19/61 of responding high-risk MDS patients, even in the IPSS high risk cytogenetic group. This has been confirmed in a recent randomized trial of decitabine vs best supportive care, which showed a trend towards longer median time to AML progression or death, although no significant survival advantage of decitabine treatment could be demonstrated. Higher complete response rates (using the less demanding modified IWG response criteria) ranging from 21 to 39% using three different dose schedules of decitabine were obtained in a recent randomized single centre trial.

With decitabine, best response was obtained after a median number of 3 courses, underscoring the importance of continuing hypomethylating treatment even if no response can be observed after a few courses.

Status
Decitabine is approved by FDA and commercially available in the US (Dacogen©). Decitabine is not commercially available in most countries in Europe and the decision from EMEA is pending.

Indication
- MDS patients with significant cytopenia
- IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other possible treatment modalities have failed)
- Not candidates for curative treatment or induction chemotherapy

Treatment Decitabine
- Decitabine 15 mg/m² by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks.
- Evaluate response (bone marrow assessment) after 4 courses unless there is overt progression earlier
- Continue treatment until progression, even in the absence of haematological improvement.

Recommendation
Decitabine: Cannot be made until approval within EU
Thalidomide

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

Status
Not approved for MDS. Larger studies ongoing.

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

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

Lenalidomide

Background
Lenalidomid is an immunomodulatory drug (IMiD) and a thalidomide structural analogue. One small and one large phase II study have shown high response rates in epo-refractory low and INT-1 risk MDS patients with a 5q deletion. Transfusion independency was achieved in 67% of the patients and the median duration of response was 116 weeks. A cytogenetic response was seen in 73% of the patients. In this study severe (grade III-IV) neutropenia and thrombocytopenia occurred in approximately 50% of the patients. The full spectrum of side effects is yet to be determined in ongoing studies. In non 5q-, low risk MDS, 26% obtained transfusion independency with a median response duration of 41 weeks.
Later updates (List et al EHA Education program 2008) report that the predicted survival in patients not obtaining a complete or partial (>50%) cytogenetic response have an overall poor outcome regarding AML evolution and survival, and that the actuarial AML rate in patients without a response is high. 60% of responding patients relapse in anemia, of yet unknown reasons in those who do not evolve to AML.

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

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

List of other therapeutic options currently in clinical trials
Arsenic trioxide. Minor effect, not recommended as single drug
Farnesyl transferase inhibitors. Minor effect, not recommended as single drug
Clofarabine. Ongoing
Inhibitors of angiogenesis. Ongoing
Thrombopoietic agents (study ongoing with AMG 531)
Chronic myelomonocytic leukaemia

Background
Chronic myelomonocytic leukaemia is a rare disease with an incidence of 3/100.000/year in a population > 60 years, M:F ratio is 2:1, median age of presentation is 65-75 years. 15-20% transforms to AML. In the laboratory findings, there should be a persistent monocytosis of >1x10^9 per liter with a percentage of monocytes >10% of WBC, not due to other causes. The patient should be BCR-ABL negative. Clonal abnormalities can be found in 20-40% of cases, but none is specific for CMML.

In 1994, the FAB group proposed to separate CMML in a proliferative form with white cell counts >13 x 10^9/L, and a dysplastic form with white cell counts below 13 x 10^9 /L. No significant difference in risk was seen between the two groups. The WHO 2008 classification divides CMML into two groups based on the number of blasts: CMML 1: < 10% medullary blasts and <5% peripheral blasts, CMML 2: 10-19% blasts and /or 5-19% peripheral blasts, with a median survival of 18 vs. 12 months for CMML 1 and 2, respectively.

Different scoring systems have been proposed. IPSS is not the best in CMML. Other scoring systems have been validated; the Spanish Score, the Düsseldorf Score, The Bournemouth Score and the MDAP Score. Risk factors associated with shorter survival are haemoglobin level below 120 g/L, platelets below 100x 10^9 /L, WBC counts above 10x 10^9 /L, presence of immature myeloid cells in peripheral blood, absolute lymphocyte count above 2,5 x 10^9 /L. Presence of bone marrow blasts above 10% were also significantly associated with shorter survival. According to the Spanish score LD>1,5 x UNL has a significant negative impact on the prognosis.

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

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

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

Allogeneic stem cell transplantation
Allogeneic stem cell transplantation remains the only option for cure in CMML, but still, the TRM is relatively high (25-41%). Allogenous SCT with reduced intensity does not have a higher relapse rate than full conditioning regimen, and the TRM rate were not higher for CMML than for other types of MDS (observation based on limited number of patients). For selected suitable patients, allogenous SCT is a treatment option to be discussed with the local transplant centre.

Recommendation allogeneic SCT and RIC
See the general discussion on allogeneous SCT page 22.
Hydroxyurea
One randomized trial with Hydroxyurea (HU) vs. VP 16 showed superiority in response (60% vs. 36%). Survival in the HU arm were 20 months vs. 9 months in the VP 16 arm. The responses were, however, short. Hydroxyurea is recommended as first-line treatment for elderly patients with a low (<10%) marrow blast count and for which the main aim is to reduce symptoms and not to prolong survival. For these patients side effects of HU are clearly milder than for azacytidine. In case of no response to HU or signs of progression of the disease, consider azacytidine as second-line treatment (see below).

Recommendation:
Recommendation level IIa, grade B

Azacytidine

Background
Both FDA and EMEA have approved 5-azacytidine for treatment of IPSS INT-2 and HR MDS and MDS/AML with 20-30% blasts in patients not eligible for haematopoietic stem cell transplantation and CMML with 10-29% marrow blasts without a myeloproliferative disorder. Azacytidine is recommended by EMEA. Decitabine has no EMEA approval. There are no studies specifically designed for CMML, but there are reviews that have analyzed the CMML cohort within larger studies. Generally but based on small patient numbers, CMML responds well to both 5-azacytidine and decitabine. For CMML with an increase of blasts and for which there is an aim to prolong survival, 5-azacytidine is recommended as 1st line treatment. Treatment should be planned to given for at least 6 cycles.

Recommendation:
Recommendation grade A, evidence level 1b.

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

See www.nordicmds.org

NMDSG02B (Induction chemotherapy followed by azacytidine in CR. For patients with high risk MDS not candidates for curative approaches). Closed for inclusion.

NMDSG02A (Treatment of the anemia in MDS with darbepoetin. For patients low risk MDS, age > 65 y). Closed for inclusion.
NMDSG07A: A multicentre phase II study of the efficacy and safety of lenalidomide in high-risk myeloid disease (high-risk MDS and AML) with a karyotype including del(5q) or monosomy 5. Closed for inclusion.

AML17, UK NCRI trial for treatment of advanced MDS and AML patients (including MDS-AML) 18-60 years of age. Only open for inclusion in 5 Danish Centers.

AML16, UK NCRI trial for treatment of advanced MDS and AML (including MDS-AML) for patients above the age of 60 years. Divided in an intensive and a non-intensive part including nonmyeloablative SCT for patients with a matching donor. Open in 5 Danish centers.

A Randomized, Double Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim Treatment of Thrombocytopenia in Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS). Trial conducted by Amgen. Ready for inclusion early 2009 in 5 Danish Centers.

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**References**

**Diagnosis and supportive care**


Epo+G-CSF treatment


**ATG+CyA**


**Allogeneic transplantation**


Azacitidine


AML like chemotherapy


**Low dose chemotherapy**


Treatment alternatives which are not commercially available or of uncertain usefulness


Chronic myelomonocytic leukemia


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


