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

Nordic MDS Group

9th update, November 2019
MDS and CMML Guidelines

WRITING COMMITTEE ................................................................................................................ 4
CONTACT INFORMATION ........................................................................................................... 4
EVIDENCE LEVELS AND RECOMMENDATION GRADES ................................................... 5
DIAGNOSTIC WORKUP OF SUSPECTED MDS ................................................................. 5
   TABLE 2. 2016 REVISION TO THE WHO CLASSIFICATION OF MDS ................................. 6
   TABLE 3. 2016 REVISION TO WHO CLASSIFICATION OF MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS ................................................... 7
PROGNOSIS .................................................................................................................................... 10
   IPSS FOR MDS (INTERNATIONAL PROGNOSTIC SCORING SYSTEM) ................................. 10
   REVISED IPSS (IPSS-R) ........................................................................................................ 11
   SIMPLIFIED RISK CATEGORIES (IPSS AND IPSS-R) ........................................................ 11
   ADDITIONAL PROGNOSTIC FACTORS ................................................................................ 12
   RECOMMENDATION FOR DIAGNOSIS AND PROGNOSIS ................................................ 13
INTERNATIONAL WORKING GROUP (IWG) MODIFIED RESPONSE CRITERIA ...... 15
THERAPEUTIC INTERVENTION AND FOLLOW UP OF MDS........................................... 16
   ALGORITHM FOR TREATMENT OF SYMPTOMATIC LOW-RISK MDS ................................. 16
   ALGORITHM FOR TREATMENT OF PATIENTS WITH HIGH-RISK MDS ............................... 16
SUPPORTIVE CARE .................................................................................................................... 17
   TRANSFUSION ........................................................................................................................ 17
   IRON CHELATION .................................................................................................................. 17
   THROMBOCYTOPENIA .......................................................................................................... 18
   TREATMENT AND PREVENTION OF INFECTIONS ............................................................ 19
TREATMENT OF LOW-RISK MDS ............................................................................................ 20
   TREATMENT OF ANEMIA WITH ERYTHROPOIESIS STIMULATING AGENTS ..................... 20
   TABLE 8. PREDICTIVE SCORE FOR RESPONSE TO ERYTHROPOIESIS STIMULATING AGENTS ............. 20
   IMMUNOSUPPRESSIVE TREATMENT ............................................................................... 22
   LENALIDOMIDE .................................................................................................................... 23
ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) IN MDS ............................................ 24
   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 .......................................... 25
   HEMATOPOIETIC CELL TRANSPANTATION COMORBIDITY INDEX (HCT-CI) ....................... 26
   TREATMENT OF HIGH-RISK MDS AND MDS/AML IN PATIENTS NOT ELIGIBLE FOR ALLOGENEIC STEM CELL TRANSPLANTATION ..................................................... 27
      AZACITIDINE ...................................................................................................................... 27
      AML LIKE CHEMOTHERAPY ............................................................................................... 28
      LOW DOSE CHEMOTHERAPY ............................................................................................. 29
CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML) ............................................................... 30
   TABLE 10. CPSS SCORE ......................................................................................................... 31
   TABLE 11. CMML GENETIC SCORE AND CPSS-MOL ......................................................... 31
   ALGORITHM FOR TREATMENT OF PATIENTS WITH CMML .............................................. 32
   ALLOGENEIC STEM CELL TRANSPLANTATION IN CMML ................................................ 33
   AZACITIDINE ....................................................................................................................... 33
Introduction

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

Writing committee

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

Contact information

Comments can be directed to sara.von.bahr.greback@ki.se or directly to one of the committee members.

News in issue 9

We have updated the interpretation of NGS-data for MDS and CMML in diagnostic work-up and prognostic evaluation. The section on allogeneic stem cell transplantation is updated.
Evidence levels and recommendation grades

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

Table 1.
Levels of evidence

<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 randomized trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomized controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomization</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>

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 randomized 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 randomized 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 evidence of bone marrow dysplasia in patients with clinical signs of impaired hematopoiesis manifested by cytopenia defined using standard laboratory values for cytopenias (Hb <130 g/L [males], <120 g/L [females], ANC <1.8 × 10⁹/L, platelets <150 × 10⁹/L). Immunophenotyping by multiparameter flow cytometry is a valuable tool for the detection of aberrant antigen expression patterns or pathological blast populations at diagnosis and during follow-up. Chromosomal aberrations are detected in approximately 50% of newly diagnosed MDS and should be performed in all cases with suspected MDS.
Detection of mutations with next-generation sequencing may provide important additional information. The diagnosis of MDS requires integration of all findings.

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

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

MDS-EH, MDS with excess blasts; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single-lineage dysplasia; MDS-SLD, MDS with single-lineage dysplasia; MDS-U, MDS, unclassifiable; SLD, single-lineage dysplasia.<sup>a</sup> Cytopenias defined as hemoglobin concentration < 100 g/L, platelet count < 100 x 10^9 cells/L, and absolute neutrophil count < 1.8 x 10^9 cells/L. Rarely, MDS can present with mild anemia or thrombocytopenia above these levels; PB monocytes must be < 1
Table 3. The 2016 revised WHO classification of myelodysplastic/myeloproliferative neoplasms in adults

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic myelomonocytic leukemia (CMML)</strong></td>
<td>Peripheral blood monomyelosis &gt; 1x10⁹/L</td>
<td>Dysplasia in one or more myeloid lineage² &lt; 20 % blasts ²</td>
</tr>
<tr>
<td></td>
<td>Not meeting WHO criteria for BCR/ABL1-positive chronic myeloid leukemia (CML), primary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>myelofibrosis (PMF), polycythemia vera (PV) of essential thrombocythemia (ET) ¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No rearrangement of PDGFRA, PDGFRB or FGFR1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 20 % blasts ²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and an acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells ³ OR the monocytosis (as previously defined) has persisted for at least 3 months and all other causes of monocytosis have been excluded</td>
<td></td>
</tr>
<tr>
<td><strong>Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML)</strong></td>
<td>Leukocytosis, neutrophilia</td>
<td>Hypercellular BM with granulocytic proliferation and granulocytic dysplasia with or without dysplastic erythroid and megakaryocytic lineages &lt; 20 % blasts in PB and BM</td>
</tr>
<tr>
<td></td>
<td>Neutrophilic dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils and their precursors ¹0 % of leukocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No BCR-ABL1 fusion gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence of PDGFRA, PDGFRB or FGFR1 rearrangement or PCM1-JAK2 (should be specifically excluded in cases with eosinophilia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No or minimal basophilipia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytes &lt; 10% of leukocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not meeting WHO criteria for PMF, PV or ET ⁴</td>
<td></td>
</tr>
<tr>
<td><strong>Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)</strong></td>
<td>Anemia</td>
<td>&lt; 1 % blasts in PB and &lt; 5 % blasts in BM</td>
</tr>
<tr>
<td></td>
<td>Persistent thrombocytosis &gt; 450 x 10⁹/L</td>
<td>Dyserthropoiesis in the BM with ring sideroblasts &lt; 15 % of erythroid precursors ³ Abnormal megakaryocytes as observed in PMF or ET</td>
</tr>
<tr>
<td></td>
<td>Presence of SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features ⁶. No BCR-ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB or FGFR1; or PCM1-JAK2; no t(3;3)(q21;q26),inv(3)(q21.3q26.2) or del(5q) ⁷</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No preceding MPN, MDS (except MDS-RS), or other type of MDS/MPN</td>
<td></td>
</tr>
<tr>
<td><strong>Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)</strong></td>
<td>Mixed MDS and MPN features</td>
<td>Mixed MDS and MPN features &lt;20 % blasts</td>
</tr>
<tr>
<td></td>
<td>No prior diagnosis of MDS or MPN</td>
<td></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 or rearrangements of PDGFRA or PDGFRB</td>
<td></td>
</tr>
</tbody>
</table>

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

Next generation sequencing (NGS), mutations in > 40 myeloid genes have recently been detected in approximately 90% of MDS patients⁵,⁶. The most frequently mutated genes are summarized in Table 12.
Mutational screening by NGS of genes commonly mutated in myeloid malignancies is emerging as an integral part of the diagnostic work-up and in prognosis evaluation. In younger individuals (< 50 years) the possibility of congenital or hereditary conditions must be considered, especially in the presence of a positive family history, concomitant physical abnormalities (nail dystrophy, facial abnormalities) or unexplained liver/pancreas/pulmonary affections. These conditions include Congenital Dyserythropoietic Anemias (CDA), Telomere-associated syndromes including Congenital Dyskeratosis, Hereditary Sideroblastic Anemia, Fanconi Anemia (FA), Congenital Neutropenias (Kostmann, Schwachman-Diamond), Diamond-Blackfan Anemia (DBA), familial platelet disorders including those with RUNXI mutation, and GATA2-mutations. For more information, please see Nordic guidelines Germline predisposition to myeloid neoplasms: Recommendations for genetic diagnosis, clinical management and follow-up.

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

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

Morphology
Diagnostic work-up requires evaluation of bone marrow and peripheral blood smears for the assessment of dysplasia and percentage of blasts and presence of ring sideroblasts together with histological examination of a bone marrow biopsy or clot, according to the WHO 2016 classification. Repeated bone marrow examinations within a few weeks or months may be necessary to establish the diagnosis of MDS and to identify cases with rapid disease progression. In case of adverse genetics, severe pancytopenia or increased blast counts, treatment should not be postponed by an additional bone marrow examination.
- Significant dysplasia within at least one lineage (erythro-, granulo-, or megakaryopoiesis), and is defined as ≥ 10 % of cells with dysplastic features; a threshold of 30 % is recommended for megakaryocytes. Megakaryocyte dysplasia should be based on the evaluation of ≥ 30 % megakaryocytes.
- Blast count should be based on evaluation of at least 500 nucleated bone marrow cells (including erythroid precursors) and a 200-leukocyte differential count in peripheral blood.
- Marrow histology/immunohistochemistry: Evaluation of marrow sections provides additional information including cellularity, evidence of fibrosis, and altered marrow architecture or the presence of focal infiltrates. Immunohistochemistry for CD34 and p53 is recommended at
diagnosis and at follow-up. The presence of cells with strong nuclear p53 staining may indicate an underlying TP53 mutation.

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

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

Clonal hematopoiesis is gradually more prevalent in with increasing age and may be present in the absence of cytopenias (CHIP). The expanding clones typically harbor similar mutations observed in myeloid disorders and carries a variable risk of evolving to MDS. These patients should be monitored, and the number of mutations and variant allele frequency (VAF) are useful predictors of risk of progression (Table 4). Unexplained cytopenias without significant dysplasia or evidence of clonal hematopoiesis are classified as Idiopathic Cytopenia of Undetermined Significance (ICUS). The somatic mutation analysis is highly informative in the diagnostic work-up of unexplained cytopenia, having high positive and negative predictive values for myeloid neoplasms. The detection of mutation in ≥ 1 genes, a VAF ≥ 0.10 and a mutation in the genes SF3B1, SRSF2, ZRSR2 or U2AF1 as well as certain co-mutations together with mutations in TET, ASXL1 or DNMT3A have significant positive predictive value and the absence of all these a high negative predictive value.

**Table 4. Comparison of genetic characteristic between CHIP, CCUS and MDS**

(adapted from Bejar)

<table>
<thead>
<tr>
<th>CHIP</th>
<th>CCUS at diagnosis</th>
<th>CCUS prior to MDS/AML progression</th>
<th>MDS all risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly mutated genes</td>
<td>DNMT3A, TET2, ASXL1, PPM1D, JAK2, TP53</td>
<td>TET2, DNMT3A, ASXL1, SRSF2, TP53</td>
<td>TET2, SRSF2, ASXL1, U2AF1, DNMT3A</td>
</tr>
<tr>
<td>Mean number of mutations</td>
<td>~1</td>
<td>~1.6</td>
<td>~2</td>
</tr>
<tr>
<td>Typical VAF</td>
<td>9-12%</td>
<td>30-40%</td>
<td>40%</td>
</tr>
<tr>
<td>Incidence</td>
<td>10-15% in 70-year olds</td>
<td>35% of ICUS</td>
<td>90% of ICUS</td>
</tr>
<tr>
<td>Risk of progression to MDS</td>
<td>0.5-1 % risk of transformation to a hematologic neoplasm</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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

**Differential diagnosis:**
The diagnosis of MDS may be difficult, in particular in patients with less than 5 % bone marrow blasts and borderline dysplasia. No single morphologic finding is diagnostic for MDS and it is...
important to keep in mind that MDS sometimes remains a diagnosis of exclusion. Differential diagnoses to be considered:

- B12 / folate deficiency
- Recent cytotoxic therapy
- HIV/HCV/HBV/Parvovirus B19/CMV/EBV-infection
- Anemia of chronic disease
- Autoimmune cytopenia
- Chronic liver disease
- Excessive alcohol intake
- Exposure to heavy metals
- Drug-induced cytopenias
- Other stem cell disorders incl. acute leukemia (with dysplasia or megakaryoblastic leukemia), aplastic anemia, myelofibrosis (in case of MDS with marrow fibrosis) and paroxysmal nocturnal hemoglobinuria (PNH)
- Other cancers infiltrating the bone marrow
- Congenital cytopenias/bone marrow failure disorders

**Prognosis**

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


<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>

<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>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>0</td>
</tr>
<tr>
<td>&lt;5</td>
<td>5-10</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias*</td>
<td>0/1</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)

(Greenberg et al., 2012). Based on 7012 untreated patients excluded s/t-MDS and CMML with leukocyte count >12 x10⁹/l. Follow this link to perform online IPSS-R scoring: http://nmds.hematology.dk/index.php/guidelines

Table 6. IPSS-R prognostic groups and score values

<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%/3%)</td>
<td>-Y, del(11q)</td>
<td>5.4</td>
<td>NR</td>
</tr>
<tr>
<td>Good (72%/66%)</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%/19%)</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%/5%)</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%/7%)</td>
<td>Complex: &gt; 3 abnormalities</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Risk group

<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)</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.

IPSS-R can be simplified into three risk groups, namely “low risk” including very low and low risk groups, “intermediate risk” and “high risk”, the latter consisting of high and very high risk groups. Use of additional differentiating features could be of particular value for categorization of IPSS-R intermediate risk patients.

**Additional prognostic factors**

- **Comorbidity**
  - MDS-specific comorbidity index (MDS-CI)\(^{15}\) is based on: cardiac, liver, renal, pulmonary disease and solid tumors.
- **Fibrosis**
  - Bone marrow fibrosis grade 2 and 3 confers an inferior prognosis.
- **Mutations associated with poor prognosis**
  - TP53, EZH2, ETV6, RUNX1, NRAS and ASXL1\(^9\). Several mutated genes are linked to specific clinical risk factors.
- **Mutations associated with higher bone marrow blasts and thrombocytopenia:** TP53, RUNX1, ASXL1, SRSF2 and NRAS,
- **TP53** mutation is associated with lower neutrophil counts and complex karyotype
- **SF3B1** mutation is associated with ring sideroblasts and a trend towards longer survival.
- **Dynamics of the disease** (progressive disease e.g. increase of bone marrow blast percentage, progression of cytopenia, clonal evolution)

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

- Mutations in TP53, EZH2, RUNX1, ETV6, and ASXL1 associate with higher risk than predicted by IPSS and IPSS-R while mutations in genes such as CBL, PRPF8, EZH2, PTPN11 and NF1 have adverse prognostic associations independent of IPSS-R.
- Mutations in ASXL1, SRSF2, U2AF1 and SF3B1 have a prognostic significance thus only in patients with <5% blasts, while their prognostic significance is lost at higher blast counts (Figure 1)\(^{10}\). Additionally, the number of pathogenic variants in a patient has been found to be prognostically significant\(^6,9,16,17\).
A lot of work remains to outline the clinical relevance of the mutational pattern of MDS. Mutational screening has in many centers become a part of the routine work up, and we recommend that it should be performed when the patient is candidate for allogeneic stem cell transplantation and in borderline cases.

**Recommendation for diagnosis and prognosis**

- All patients should be classified according to WHO 2016 classification.
- All patients should be risk stratified according to IPSS and IPSS-R.
- We recommend assessment of additional prognostic features, such as bone marrow fibrosis, co-morbidity and molecular genetics, as well as p53 analysis by immunohistochemistry or sequencing.
- MDS should be reported to the National Cancer registries in all Nordic countries and to MDS specific registries, if applicable.
Figure 2. Enrichment of mutations in sAML and high risk MDS versus high-risk and low-risk MDS respectively. Enrichment of mutations expressed as odds ratio (OR) of mutation rates in s-AML vs high risk MDS (x-axis) and in high risk MDS vs low risk MDS (y-axis). Non-significant OR are represented by black circles. Adapted from 18.
International Working Group (IWG) modified response criteria

The IWG criteria\(^{19}\) define four aspects of response based on treatment goals: (1) altering the natural history of disease, (2) cytogenetic response, (3) hematological improvement (HI), and (4) quality of life.

For clinical trials, please see revised criteria (PMID: 30404811).

Table 7.
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 \leq 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>( \text{Hb} \geq 110\ \text{g/L}, )</td>
</tr>
<tr>
<td></td>
<td>( \text{Platelets} \geq 100 \times 10^9/\text{L}, )</td>
</tr>
<tr>
<td></td>
<td>( \text{Neutrophils} \geq 1.0 \times 10^9/\text{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 \geq 50% over pre-treatment but still \geq 5%</td>
</tr>
<tr>
<td></td>
<td>Cellularity and morphology not relevant</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>BM \leq 5% myeloblasts and decrease by \geq 50% over pre-treatment</td>
</tr>
<tr>
<td>Stable disease</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 \geq 50% from maximum remission/response levels in granulocytes or platelets</td>
</tr>
<tr>
<td></td>
<td>Reduction in Hb concentration by \geq 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>\geq 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 \geq 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>Haematological 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 \geq 15g/L Relevance of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for Hb \leq 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 \geq 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 x10^9/L</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 a candidate for therapeutic intervention at disease progression, regular bone marrow analysis is recommended. However, it should be pointed out that the primary WHO classification of MDS should not be changed on the basis of follow-up bone marrow examination but the changes should be interpreted as e.g. progression of transformation.

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

Algorithm for treatment of symptomatic low-risk MDS

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

Algorithm for treatment of patients with high-risk MDS

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

Transfusion

A recent study suggests that quality of life is improved with higher target Hb levels for transfusion\textsuperscript{20}. 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, considering co-morbid illness as well as quality of life issues. No universal trigger or target for transfusion is recommended.

**Platelet transfusions:** Please see thrombocytopenia section.

Iron Chelation

**Background**
There are currently three different iron chelators available, Desferrioxamine (DFO) to be given preferably by iv or sc infusion, and Deferasirox and Deferiprone, both given orally, the latter only available in some Nordic countries. A large prospective phase 2 trial has been conducted in which 341 patients with MDS were treated with deferasirox for one year\textsuperscript{21}. Reduction in median ferritin level and labile plasma iron was observed, and the drug was generally well tolerated with gastrointestinal side effects and impairment of renal function most frequently reported. There are no studies proving the effect of iron chelation on long-term outcome in MDS. No randomized trials comparing the efficiency of the different iron chelators have been conducted in MDS. In practice, oral chelation is generally the first choice, and if not efficient or tolerable treatment could be changed to desferrioxamine.

The goal of the treatment is to achieve a safe tissue iron concentration by promoting negative iron balance and iron detoxification.

**Indication:**
- Iron chelation is recommended in patients for whom long term transfusion therapy is likely, generally meaning patients with low and INT-1 IPSS-score (Very low and Low risk in IPSS-R). Start treatment when S-Ferritin > 1500 µg/l, or after approximately 25 units red cell transfusions.
- For transfusion-dependent patients that may be candidates for a future allogeneic transplantation it is crucial to avoid iron overload, and iron chelation should then be considered preventive and be initiated at an earlier stage.

**Monitoring iron chelation:**
- The target Ferritin level is <1000 µg/l.
Parenteral chelators

**Desferrioxamine (DFO) treatment**
- 40 mg/kg (20-50 mg) by subcutaneous infusion over 8-12 hours 5-7 days per week.
- Alternatively give DFO 5-10 g via portable infusion pump in a venous port over 5 days when the patient receives blood transfusion.
- Vitamin C 2-3 mg/kg/d could be started 4 weeks after the onset of DFO therapy to improve iron excretion. Caution, higher doses may be associated with cardiac arrhythmia.
- Continuous (uninterrupted) 24-hour DFO should be considered in patients at high risk, e.g. with Ferritin persistently > 2500 µg/l and significant cardiac disease.
- In case of severe iron overload with insufficient effect of DFO, it can be combined with deferiprone or deferasirox in usual doses.

**Recommendation:**
Recommendation grade B, evidence level III.

Oral chelators

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

**Recommendation:**
Recommendation grade B, evidence level IIA

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

**Recommendation:**
Recommendation grade B, evidence level III.

Thrombocytopenia

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

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

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

**Decision-making and treatment**

- Platelet transfusion is recommended in thrombocytopenic patients with moderate or severe bleeding. A universal trigger value or prophylactic platelet transfusions is not recommended as a rule.
- Tranexamic acid 500-1000 mg times 3-4 daily orally (or intravenously if severe bleedings) can be used for patients that are thrombocytopenic and actively bleeding.

**Recommendation:**
Recommendation grade C, evidence level IV.

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

**Thrombopoietin (TPO) receptor agonists**

Thrombopoietin (TPO) receptor agonists romiplostim (Nplate) and eltrombopag (Revolade) are approved for the treatment of immunological thrombocytopenic purpura (ITP). They have also been tested in several clinical studies for thrombocytopenic MDS patients, both as monotherapy and in combination with myelosuppressive drugs, with the aim of less bleedings, less need for platelet transfusions and better overall outcome given the possibility to administer treatment in full doses without delays. A Cochrane review\(^2\) did not find enough evidence for recommending neither romiplostim nor eltrombopag in MDS.

**Treatment and prevention of infections**

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

G-CSF treatment

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

Treatment of low-risk MDS

Treatment of anemia with erythropoiesis stimulating agents

Background

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

Indication for treatment

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

Table 8. Predictive score for response to erythropoiesis stimulating agents

<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>≥2 units RBC / month</td>
<td>1</td>
<td>≥500 U/l</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Response criteria for evaluation of erythroid response

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

- Complete erythroid response (CER)
  - Stable hemoglobin ≥115 g/l

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

- Verified MDS diagnosis
MDS and CMML Guidelines

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

Dosing of erythropoiesis stimulating agents

- **Target hemoglobin level <120 g/l**
- **Induction phase:**
  - **EPO:** Start with EPO 30 000 U/week (reduce initial dose if impaired renal function or low body weight). Increase to 30 000 twice weekly if no response after 8 weeks. Doses higher than 60 000 U/week are not recommended.
  - **DAR:** Start with 300 µg/14 days or 150 µg/week (reduce initial dose if impaired renal function or low body weight). Increase to 300 µg/week if no response after 8 weeks.
    - Avoid starting with 300 µg/week, since this may result in a rapid increase in Hb-level to supra normal levels for a period of time due to the extended half-life of DAR. Supra normal Hb-level is associated with increased risk of thrombosis.
  - **G-CSF:** Add if no response to 8 weeks of full dose EPO or DAR. Start with 300 µg (or equivalent) once weekly, alternatively 120 µg 2-3 times a week. Aim at a clear rise in neutrophil count (to 6-10 x 10⁹/l). Maximum dose 300 µg x 3 times a week.
    - Long-acting G-CSF has not been evaluated in MDS and cannot be recommended.
  - **Overdose:** If Hb-levels increase above upper normal limit then interrupt the growth factors and consider venesectio; resume treatment at a lower dose when Hb falls below 120 g/l.
- **Maintenance phase:** In case of CER, decrease the dose every 8 weeks, by reducing the dose per injection or increasing the dosing interval (in particular when using DAR). Median dose of EPO is 30 000 U/week, although some patients maintain their response on weekly doses of 5000-10 000 U.
  - Monitor ferritin regularly, consider supplementation of oral or iv iron if ferritin falls below upper normal limit, in particular when there are signs of functional iron deficiency (low MCHC in absence of microcytosis).
- **Lost response:**
  - Evaluate for iron and vitamin deficiencies.
  - Increase the dose of EPO or DAR. If no response at maximum dose, then add G-CSF and evaluate after maximum of another 8-(16) weeks.
  - Bone marrow examination is recommended if response cannot be rescued or in case of clinical signs of disease progression (18-28 % of patients show signs of disease progression at time of lost response).

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

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

**Recommendation DAR±G-CSF**
Recommendation grade B, evidence level IIa.
Immunosuppressive treatment

Background
Several international studies have demonstrated response rates in the order of 30% to immunosuppressive therapy (antithymocyte globulin (ATG) in some investigations combined with cyclosporine A (CyA)) in patients with MDS-SLD and MDS-MLD. Hypoplastic bone marrow, good and intermediate karyotype, HLA-DR15 positivity, young age, treatment within 2 years from diagnosis and short duration of red cell transfusion dependence predict for a response to immunosuppressive therapy in MDS patients. In aplastic anemia, ATGAM has been proven superior to other ATG, but this has not been investigated in MDS. Retrospectively, serum sickness was reported in 18% and significantly higher with rabbit-ATG. To date, there are no controlled data to support the addition of cyclosporine A to ATG treatment in MDS, although this combination has been shown to increase the response rate from 27% to 51% in a retrospective analysis.

Decision-making and treatment with ATG

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

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

Treatment
- There are different ATG products available, and ATG should be used according to local traditions/experience, for example horse ATG, Pfizer (ATGAM™); 40 mg/kg, d 1-4
- Prednisolone: During treatment with ATG, we recommend the addition of prednisolone day 1-24 (1 mg/kg/day d 1-10), then tapering the dose for the following 14 days until a complete stop.
- Prophylaxis with sulfamethoxazole/trimethoprim for 6 months is recommended.
- Consider prophylaxis with fluconazole and acyclovir.

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

Recommendation ATG
Recommendation grade B, evidence level Ib.

Cyclosporine A treatment
MDS and CMML Guidelines

- It is up to the treating physician to decide whether to include CyA, as maintenance treatment in the immunosuppressive treatment. No sufficient published evidence for MDS.
- In case of contraindications to ATG, therapy with cyclosporine A alone can be tried. Dosage according to local recommendations (serum CyA around 200 ng/ml is recommended, adjust according to creatinine levels).

**Recommendation CyA**
Recommendation grade B, evidence level III.

**Lenalidomide**

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

**Decision-making and treatment considerations**

- **Eligible patients**
  - Lower risk MDS with isolated del(5q) that have failed EPO or are not considered candidates according to the predictive model
  - No p53 alteration (TP53 mutation by deep sequencing of presence of >2% of marrow cells with strong p53 staining); such patients should be evaluated for alternative treatments due to their adverse prognosis and lenalidomide should only be considered in frail patients where no suitable alternative is available

- **Non eligible patients**
  - Candidates for allo SCT; if lenalidomide is given in selected transplant candidates it should only be in the absence of p53 alterations, with careful monitoring for signs of disease progressions of disease progression.

- **Dosing**
  - Repeated courses of 10 mg daily for 21 days followed by a 7-day break.
  - In elderly frail patients or patients with renal impairment consider 5 mg 21 of 28 days.

- Prior to lenalidomide treatment, patients should be informed about the increased risk of other malignancies observed in multiple myeloma patients
- Lenalidomide is not recommended for non del(5q) MDS or advanced MDS, unless in a clinical trial
- Sexually active, fertile patients must use effective contraception

**Recommendation Lenalidomide**
Recommendation grade A, evidence level 1b.
Allogeneic stem cell transplantation (SCT) in MDS

**Background**

Allogeneic stem cell transplantation is the only known curative treatment option in patients with MDS. The outcome after allogeneic transplantation is very heterogeneous and the prognosis has been related to several different prognostic factors. Relapse is the most significant cause of death with an overall relapse rate (RR) about 30%. The overall transplant related mortality (TRM) has been reported to be 5-20%. Several non-randomized and a few randomized 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 often different with more relapses in the RIC SCT patients, but a 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%.

**Poor risk factors for TRM:**
- Age
- Advanced disease stage
- Therapy related MDS
- Sub-optimally matched unrelated donor
- Female donor to male patient
- High comorbidity score.
- Karnofsky < 70

**Risk factors for relapse:**
- Age
- Advanced disease stage
- Long disease duration
- Severe marrow fibrosis
- Complex karyotype and especially in the presence of mutated TP53

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.

Several non-randomized studies and a few randomized have compared reduced intensity conditioning (RIC) with conventional myeloablative conditioning (MAC) transplantation. Most of the studies describe similar overall survival. The causes of treatment failure, however, are often different with more relapses in the RIC SCT patients, but with a higher TRM in patients receiving MAC. Results have improved during the last decade and more elderly patients have been eligible.
for transplantation 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 %31. In a randomized study Treo/Flu has been shown to have a survival advantage compared to RIC Flu/Bu38.

Decision making and treatment

Indications (sibling or unrelated)
- All fit patients without comorbidities should be considered for allogeneic SCT. There is no specific age limit, but age should be taken into consideration. The indication should be assessed in association with donor availability, eventual co-morbid conditions and functional status (see comorbidity index) and cytogenetic and molecular mutational status.
- IPSS-R high and very high risk. For intermediate risk and for some patients with low risk additional poor risk factors such as life-threatening cytopenias, high transfusion burden, poor-risk cytogenetics/molecular characteristics and blast increase may indicate a need for an early SCT.

Cytoreductive chemotherapy prior to SCT

Cytoreductive therapy is often given before SCT, but the value is not established due to lack of randomized trials and conclusive retrospective data25,28-30,39. In selected cases cytoreductive therapy might be the best choice, however, the increased risk of mortality and morbidity, particularly of induction chemotherapy, which may prevent SCT, should be taken into consideration.
- Patients with blast counts ≥ 10 % should be considered for cytoreductive therapy.
- Treatment should be determined in close collaboration with the local transplant team and usually involves HMA or AML like chemotherapy. Age of patient, comorbidities and cytogenetic/molecular characteristics influence the choice between HMA and induction chemotherapy.

Decision making
- At diagnosis always consider if the patient is a candidate for allogeneic stem cell transplantation. It is not recommended to wait for significant disease progression before a decision about allogeneic transplantation is taken.
- In patients < 50 years of age consider the possibility of underlying rare familial syndromes (Fanconi, telomere-associated disorders) that may have implications for the choice of conditioning regimen and donor.
- 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) and Karnofsky score.
- 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, mismatch donors or haploidentical graft) might be considered depending on age, disease, and comorbidity.
- Patients with a high transfusion burden should when possible receive appropriate iron chelation before transplantation, but the ferritin level should not postpone the transplantation.
- All transplant related procedures (conditioning, immunosuppression and supportive care) should be performed according to local guidelines. However, it is recommended to use a limited number of conditioning regimens. The selection of regimens should be discussed within each country with the transplant teams.

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

**Hematopoietic Cell Transplantation comorbidity index (HCT-CI)**

Based on Cox proportional hazard analysis of specific comorbidities in 1055 patients receiving allogeneic SCT at Fred Hutchinson Cancer Center in Seattle (294 RIC and 761 myeloablative), a Comorbidity Index was constructed that has been shown in many (but not all studies) to predict non-relapse mortality and survival. The HCT-CI has been updated and is available on the web ([http://www.hctci.org/](http://www.hctci.org/))⁴⁰. It is recommended to evaluate a potential transplantation candidate with HCT-CI prior to referral. The higher the HCT-CI, the higher is the risk for non-relapse mortality (transplantation related mortality) and the lower the overall survival. It has also been suggested that Karnofsky scores together with HCT-CI gives better prediction on the risk for TRM than either used alone.

**Table 9. HCT-CI**

<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 hypoglycemic 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>
</tbody>
</table>
### MDS and CMML Guidelines

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/severe renal</td>
<td>Serum creatinine &gt; 2 mg/dL (178 mmol/l), on dialysis, or prior renal</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>transplantation</td>
<td></td>
</tr>
<tr>
<td>Moderate pulmonary</td>
<td>DLco and/or FEV(_1) 66%-80% or dyspnea on slight activity</td>
<td>2</td>
</tr>
<tr>
<td>Prior solid tumor</td>
<td>Treated at any time point in the patient's past history, excluding non-</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>melanoma skin cancer</td>
<td></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 FEV(_1) ≤ 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 hematopoietic stem cell transplantation. Azacitidine is also approved for treatment of AML with >30% blasts in patients not eligible for hematopoietic stem cell transplantation.

A randomized phase III study of patients with advanced MDS not primarily eligible for curative treatment (SCT), compared azacitidine to best standard of care (BSC), where the treating physician could choose between best supportive care only, best supportive care with low dose cytarabine or best supportive care with AML-like chemotherapy\(^41\). 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)\(^41-47\). A total of 50% responded (CR, PR and hematological improvement = HI) to azacitidine-treatment and first response was seen in 91% of the responders within 6 cycles and best response was seen in 48% of the responders within 12 cycles, underscoring the importance of continuing treatment even if no response can be observed after a few courses\(^42,48\). Of importance is that even patients with HI only, also had an OS benefit compared to BSC i.e. CR/PR is not a prerequisite for azacitidine-treatment benefit (paradigm shift)\(^41,48,49\).

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\(^50,51\).
Based on these findings, azacitidine is generally recommended as first choice for HR-MDS and MDS/AML (with 20-30 % blasts) unless the patient is young with good prognostic features for response to AML-like chemotherapy.

**Decision making and treatment**

**Indication**
- Mainly indicated in patients who are not candidates for curative treatment, although azacitidine can also be considered when choosing bridging therapy prior to allogeneic SCT.
- MDS IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other potential treatment modalities have failed).
- MDS/AML with 20-30 % blasts.
- Expected survival exceeding 3 months.

**Azacitidine treatment**
- Azacitidine 75 mg/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 1-5 + 8-9).
- Continue treatment unless obvious signs of progression. Obvious signs of improvement are rarely observed after only 1 to 2 courses of treatment.
- Myelosuppression is very common especially during the first courses and should not lead to un-necessary pausing or dose reductions unless threatening cytopenic complications or intolerance. The use of G-CSF and/or prophylactic antibiotics could be considered.
- Evaluate response (bone marrow assessment) after 6 courses unless there is overt progression or indications of overdosing earlier. If SCT is planned, evaluate after 3 cycles or earlier if progression is suspected. Allow sufficient time (5-6 weeks) after last course before marrow evaluation (include biopsy), to avoid azacitidine induced hypoplasia/marrow suppression at time of evaluation.
- In case of response, recovery of peripheral blood values may be delayed due to suppressive effects of azacitidine. It may be useful to make an 8 weeks-pause after cycle 6 to see if recovery occurs.
- It is generally recommended to continue treatment until clear signs of loss of response or progression. Fragile and elderly patients may not tolerate treatment and may experience treatment induced marrow suppression. In such case the dose can be decreased or the dose interval increased to 5 weeks.

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

**AML like chemotherapy**

**Background**
A number of studies have been published where a total of more than 1100 patients with HR-MDS or MDS-AML have been treated with different combinations of induction chemotherapy. 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, i.e. overall survival is not affected by the treatment. There are no data to support that high dose chemotherapy with autologous stem cell support is superior to AML like chemotherapy. Hence, no recommendation can be made as to the use of autologous stem cell transplantation in younger HR-MDS and MDS-AML patients.

**Decision making and treatment**

**Indication for AML like chemotherapy**
Consider younger patients with high-risk MDS (IPSS INT-2 or HR), IPSS-R intermediate and MDS-AML
- Remission induction of younger patients prior to allogeneic SCT.
- In patients not eligible for allogeneic SCT if
  - good prognostic features for CR, i.e. normal s-LDH and/or WBC <4.0 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.
- If azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR.

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

**Recommendation AML like chemotherapy:**
Recommendation grade B, evidence level IIa.

**Low dose chemotherapy**

**Background**
There is insufficient evidence to recommend routine use of low-dose chemotherapy, since there are no data showing a beneficial effect on survival or transformation to AML in unselected groups of patients. However, in individual patients low-dose chemotherapy with melphalan or Ara-C may be used to reduce high white blood cell counts as well as bone-marrow blast counts, and to improve pancytopenia in MDS.
MDS and CMML Guidelines

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 mild61-63.
- Suggested indication: Symptomatic high risk MDS and MDS/AML patients with a normal karyotype and a hypo/normocellular bone marrow.
- Dosage: 2 mg/day until response (usually 8 weeks) or progression.

Recommendation
Recommendation grade B, evidence level IIb.

Low-dose cytosine arabinoside
One large randomized study comparing low dose cytosine arabinoside (LDAC) and supportive care in predominantly high-risk MDS patients showed a response rate of approximately 30% in the LDAC arm, but no benefit in terms of overall survival and transformation to AML64-66. 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 azacitidine41.
- 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.

Chronic myelomonocytic leukemia (CMML)

Background
Chronic myelomonocytic leukemia is a rare disease with an incidence of 3/100,000/year in the population > 60 years, male: female ratio is 2:1, median age at presentation is 65-75 years. 15-20% transform to AML. The disease has both myeloproliferative and myelodysplastic features. In 1994, the FAB group proposed to separate CMML in a proliferative form (CMML-MP) with white cell counts >13 x 10^9/L, and a dysplastic form (CMML-MD) with white cell counts below 13 x 10^9/L. The WHO 2016 classification divides CMML into three groups based on the number of blasts (including promonocytes): CMML-0: < 2 % blasts in PB and < 5 % blasts in BM), CMML-1: 2-4 % blasts in PB and 5-9 % blasts in BM), CMML-2: 5-19 % blasts in PB and 10-19 % blasts in BM).

Diagnostic criteria (according to WHO 2016): See Table 3.

In 20-40% of cases, clonal abnormalities can be found, but none is specific for CMML. Heterozygous somatic mutations are found in over 90% of patients, with a more homogenous pattern than in other MDS. TET2 mutations occur in around 60% of patients, SRSF2 in around 50% and ASXL1 in around 40% of cases. More than 80% of cases carry at least one of these three mutations. ASXL1 is so far the only mutation with a clear adverse prognosis, however the revised CPSS score CPSS-Mol takes
into account ASXL1, NRAS, SETBP1 and RUNX1. In especially the proliferative CMML, JAK2 mutation may also be present.

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

CMML specific scoring system (CPSS, Such et al\textsuperscript{68}), Table 10, defines 4 important prognostic factors including WHO subtype, FAB subtype, CMML-specific cytogenetic risk classification and transfusion dependency. Patients could be divided into 4 risk groups differing in OS and AML evolution; low risk (0 points), intermediate-1 (1 point), intermediate-2 (2-3 points) and high risk (4-5 points). The median overall survival (OS) for low, intermediate-1, intermediate-2 and high risk were: 61, 31, 15 and 9 months in the validation cohort.

**Table 10. CPSS score**

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>Points</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts (%)</td>
<td>&lt;10 % in BM and &lt; 5 % in PB</td>
<td>10-19 % in BM or 5-19 % in PB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White cell count</td>
<td>Up to 13 x 10^9/L</td>
<td>&gt; 13 x 10^9/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype\textsuperscript{°}</td>
<td>Low risk</td>
<td>Intermediate</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Transfusion dependency</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></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 (≥ 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. Red blood cell (RBC) transfusion dependency defined as having 1 RBC transfusion every 8 weeks over a period of 4 months.

**Table 11. CMML genetic score and CPSS-Mol**

(Elena et al\textsuperscript{67})

Variables and prognostic score values of the CMML genetic score

<table>
<thead>
<tr>
<th>Variable score</th>
<th>CPSS cytogenetic risk group</th>
<th>ASXL1</th>
<th>NRAS</th>
<th>RUNX1</th>
<th>SETBP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Unmutated</td>
<td>Unmutated</td>
<td>Unmutated</td>
<td>Unmutated</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>Mutated</td>
<td>Mutated</td>
<td>Na</td>
<td>Mutated</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>Na</td>
<td>Na</td>
<td>Mutated</td>
<td>Na</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic risk group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
</tr>
</tbody>
</table>

Cyogenetic risk groups are defined according to Such et al\textsuperscript{68}: low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.
Variables and prognostic score values of the CPSS-Mol

<table>
<thead>
<tr>
<th>Genetic risk group</th>
<th>BM blasts</th>
<th>WBC count</th>
<th>RBC transfusion dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
<td>&lt; 5 %</td>
<td>&lt; 13x10⁹/L</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate-1</td>
<td>≥ 5 %</td>
<td>≥ 13x10⁹/L</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate-2</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Na</td>
<td>Na</td>
</tr>
</tbody>
</table>

CPSS-Mol risk group | Score
---|---
Low | 0
Intermediate-1 | 1
Intermediate-2 | 2
High | ≥4

Genetic risk groups are defined as reported in the table above.
RBC transfusion dependency is defined according to Malcovati et al.69 and Such et al.68

This model was able to identify 4 risk groups with significantly different OS (HR = 2.69, P < .001) and cumulative incidence of leukemic evolution (HR = 3.84, P < .001) (median survival not reached, 64, 37, and 18 months; 48-month cumulative incidence of AML evolution of 0%, 3%, 21%, and 48% for the low, intermediate-1, intermediate-2, and high-risk group, respectively).67 The learning and validation cohorts consisted of 214 and 260 CMML patients, respectively67.

**Algorithm for treatment of patients with CMML**

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

1. Consider allogeneic SCT for both CMML 1 and CMML 2.
2. Patient with CMML 2 (10-19 % bone marrow blasts and promonocytes) and leukocyte count less than 13 x 10⁹/L: Azacitidine.
3. Patient with CMML 2 (10-19 % bone marrow blasts and promonocytes) and leukocyte count more than 13 x 10⁹/L but not severely elevated leukocyte counts: Azacitidine treatment can be effective (less evidence for its benefit). Alternatively hydroxyurea or AML-like chemotherapy may be given.
4. Patient with CMML 1 (5-9 % bone marrow blasts and promonocytes), leukocytes less than 13 x 10⁹/L and high-risk cytogenetics: Treatment with azacitidine should be considered if candidate for allogeneic stem cell transplantation. Otherwise: Wait and see. Can be treated with EPO according to recommendations for other low risk MDS.
5. Patient with CMML 0 (< 5 % blasts) or CMML 1 (5-9 % bone marrow blasts and promonocytes) and leukocytes more than 13 x 10⁹/L: Hydroxyurea if symptomatic, EPO if anemia.
Allogeneic stem cell transplantation in CMML

Chronic myelomonocytic leukemia is a challenging disease being difficult to cure even with allogeneic stem cell transplantation. CPSS\(^6\) was validated in 209 transplanted patients by Duong and colleagues in 2015. There was a difference in 5 years disease-free survival (DFS) between low/int-1 and int-2/high risk CPSS (26 % vs 14 %) and OS (44 % vs 18 %) respectively. Mortality from higher CPSS scores was more often related to relapse than with lower scores. Other factors that significantly predicted outcome were performance status (better when > 90 %) and graft source (better for peripheral stem cells). The long term DFS was 26 % in the whole population and only 14 % in int2-/high-risk\(^7\). In an EBMT-study with 513 CMML patients 4-years, non-relapse mortality was 41 %, RR 32 %, relapse-free survival 27 % and OS 33 %\(^7\). The only significant prognostic factor for survival in a multivariate analysis was the presence of complete remission at HSCT. Therefore, transplantation early after diagnosis or after achievement of the best possible remission with either chemotherapy is recommended\(^7\).

Somatic mutations also seem to be independent prognostic factors for CMML. An updated prognostic score of CPSS (CPSS mol) has recently been presented in Blood\(^6\). CPSS mol incorporates mutations in RUNX, NRAS, ASXL1 and SETBP in the prognostic system (Table 11).

**Indications for Allogeneic stem cell transplantation**

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

**Azacitidine**

**Background**

Both FDA and EMEA have approved 5-azacitidine for treatment of CMML with 10-29% marrow blasts without a myeloproliferative disorder (leukocyte counts below 13 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.

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

**Hydroxyurea**

One randomized trial with Hydroxyurea (HU) vs. Etoposide (VP 16) showed superiority in response (60 % vs. 36 %). Survival in the HU arm was 20 months vs. 9 months in the VP 16 arm. The responses were, however, short.
Hydroxyurea is recommended as first-line treatment for elderly patients with a low (< 10 %) marrow blast count and for which the main aim is to reduce symptoms and not to prolong survival. For these patients side effects of HU are clearly milder than with azacitidine. If the patient does not respond to HU or presents signs of progression of the disease, consider azacitidine as second-line treatment (see below).

**Recommendation:**
Recommendation grade B, level IIa.

**Treatment alternatives which are not commercially available or of uncertain usefulness**

We here report on a selected number of potential therapeutic candidates which are in clinical trials but not commercially available. We have also chosen to include information about drugs that we do not recommend, but that we know sometimes are used in MDS.

**Venetoclax**

Venetoclax is a pro-apoptotic drug approved for treatment of CLL. In the United States, it is also approved for treatment of AML in combination with hypomethylating drugs or low-dose cytarabine where prospective studies have shown high response rates. Recent data from scientific meeting abstracts report high response rates also in MDS-patients.

The drug is associated with significant hematological toxicity and the preferable dose in MDS is not yet determined. The doses used in the MDS-studies have ranged from 100-400 mg / day for 14 days every 28 days.

The clinical experience from the Nordic countries is mainly from transplantation-candidates where the drug has been used as bridging therapy.

**Recommendation:** No general recommendation. Discussion with regional MDS-representatives is recommended.

**Steroids**

Both prednisolone and anabolic steroids have been tried for MDS. Most reports are relatively old and very small, and there is no evidence of a significant response in terms of improved cytopenia. Generally, steroids should be avoided due to their side effects. According to clinical experience, MDS with a significant inflammatory component, as mirrored by high sedimentation rate, arthritis, and other inflammatory symptoms, may occasionally respond in terms of improved general symptoms to moderate doses of prednisolone.

**Recommendation:** Generally not recommended. Anecdotal non-validated reports have also shown that the thrombocytopenia of MDS occasionally may show a temporary response to anabolic steroids.
**Recommendation**: No general recommendation.

**Decitabine**

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

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

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

An EORTC study comparing low-dose decitabine to best supportive care in 233 higher risk MDS patients age 60 years or older and ineligible for intensive chemotherapy showed, that decitabine treatment resulted in improvements of OS and AML-FS (nonsignificant), of PFS and AML transformation (significant) and of patient-reported QoL parameters.

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

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

**Treatment with Decitabine**
- Decitabine 15 mg/m² by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks. Alternatively give 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 hematological improvement.
- Decitabine high dose regimen (20 mg/m²) on days 1 through 10 of 28-day cycles according to Welch et al. seems to be a potent therapy for some high risk patients, including those with TP53 mutations.

**Recommendation**: Not recommended for treatment of MDS, unless azacitidine intolerance, but can be considered in special high risk cases.
Ongoing MDS trials within the Nordic Region (including trials of the Nordic MDS Group)

See www.nmds.org

Disclosure statement

AOK: Advisory board - Novartis
LC: Nonoe
ID: Advisory board - Celgene
FE: Expert statement for Celgene, congress/travel expenses covered by Amgen and Novartis
EE: None
LF: None
HG: Honoraria from Amgen and Celgene, Advisory board – Celgene, Advisory board Incyte
MSH: None
MJ: Research grant from Celgene. Honorarium for lectures from Novartis
LK: None
EHL: Research grant for clinical trials Celgene. Advisory board - Celgene
PL: None
JMN: None
LN: Honorarium for lectures from Celgene and Novartis
AP: None
EP: None
KRJ: None
LS: None
JU: None
## Table 12. Genes frequently mutated in MDS.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Target regions</th>
<th>Types of pathogenic variants</th>
<th>Main hotspots</th>
<th>Mutational frequency</th>
<th>Mutational frequency</th>
<th>Comment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>Chromatin modification</td>
<td>Exon 13</td>
<td>Nonsense and frame-shift variants</td>
<td>p.E635fs*; p.G646fs</td>
<td>23 %</td>
<td>14 %</td>
<td>Associated with unfavorable clinical outcome in all myeloid neoplasms (MDS, MDS/MPN, MPN).</td>
<td>9,73,78</td>
</tr>
<tr>
<td>BCOR</td>
<td>Transcriptional regulation</td>
<td>Total coding region</td>
<td>Nonsense and frame-shift variants</td>
<td>p.L367fs<em>46; p.K385fs</em>47</td>
<td>4 %</td>
<td>5 %</td>
<td>Frequent in aplastic anemia</td>
<td>79,80</td>
</tr>
<tr>
<td>CALR</td>
<td>Signal transduction</td>
<td>Exon 9</td>
<td>Indels in exon 9</td>
<td>p.T618I</td>
<td>5 %</td>
<td>4 %</td>
<td>MPN</td>
<td>82,83</td>
</tr>
<tr>
<td>CSFR3</td>
<td>Signal transduction</td>
<td>Exon 14 and 17</td>
<td>Missense (E14) and truncating (E17) variants</td>
<td>p.T618I</td>
<td>5 %</td>
<td>4 %</td>
<td>Strictly associated with CNL, found in a subset of patients with aCML.</td>
<td>82-85</td>
</tr>
<tr>
<td>CBL</td>
<td>Signal transduction</td>
<td>Exon 8 and 9</td>
<td>Multiple types of pathogenic variants</td>
<td>p.R882</td>
<td>3 %</td>
<td>1 %</td>
<td>Shortened survival</td>
<td>9,92,93</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>DNA methylation</td>
<td>Exon 7 to 23</td>
<td>Multiple types of pathogenic variants mainly missense</td>
<td>SET-domain (p.R690)</td>
<td>2 %</td>
<td>1 %</td>
<td>Shortened survival</td>
<td>9,73,94,95</td>
</tr>
<tr>
<td>ETV6</td>
<td>Transcriptional regulation</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td>p.R132</td>
<td>3 %</td>
<td>3 %</td>
<td>Shortened survival</td>
<td>101-103</td>
</tr>
<tr>
<td>EZH2</td>
<td>Chromatin modification</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td>p.R140; pR172</td>
<td>4 %</td>
<td>4 %</td>
<td>Familial AML/MDS.</td>
<td>101,102,104,105</td>
</tr>
<tr>
<td>GATA1</td>
<td>Transcriptional regulation</td>
<td>Exon 2</td>
<td>Multiple types of pathogenic variants</td>
<td>AML in Down syndrome</td>
<td>96-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GATA2</td>
<td>Transcriptional regulation</td>
<td>Exon 2 to 6</td>
<td>Multiple types of pathogenic variants</td>
<td>exon 5 and 6 (ZF1 and ZF2 domains)</td>
<td>Familial AML/MDS.</td>
<td>96-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td>DNA methylation</td>
<td>Exon 4</td>
<td>Missense variants</td>
<td>p.V617F</td>
<td>5 %</td>
<td>5 %</td>
<td>No impact on survival</td>
<td>9,73</td>
</tr>
<tr>
<td>IDH2</td>
<td>DNA methylation</td>
<td>Exon 4</td>
<td>Missense variants</td>
<td>p.V617F</td>
<td>5 %</td>
<td>5 %</td>
<td>No impact on survival</td>
<td>9,73</td>
</tr>
<tr>
<td>Gene</td>
<td>Signal transduction</td>
<td>Exons</td>
<td>Multiple types of pathogenic variants</td>
<td>Mutational Hotspot(s)</td>
<td>Frequency AML</td>
<td>Frequency MPN</td>
<td>Additional Information</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------------------</td>
<td>-------</td>
<td>---------------------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>Signal transduction</td>
<td>Exons 8-14, Exon 17</td>
<td>Multiple types of pathogenic variants</td>
<td>p.D816</td>
<td>1 %</td>
<td>2 %</td>
<td>AML</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>Signal Transduction</td>
<td>Exon 2 and 3</td>
<td>Missense variants</td>
<td>p.D12, p.D13, p.D61</td>
<td>3 %</td>
<td>2 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPL</td>
<td>Signal transduction</td>
<td>Exon 10</td>
<td>Missense variant</td>
<td>p.W515L</td>
<td>3 %</td>
<td>2 %</td>
<td>MPN</td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>Signal transduction</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td></td>
<td>3 %</td>
<td>4 %</td>
<td>Familial cases, JMML</td>
<td></td>
</tr>
<tr>
<td>NPM1</td>
<td>Signal transduction</td>
<td>Exon 12</td>
<td>Insertions</td>
<td>p.W288fs*12</td>
<td>1 %</td>
<td>1 %</td>
<td>AML</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>Signal Transduction</td>
<td>Exon 2 and 3</td>
<td>Missense variants</td>
<td>p.D12, p.D13, p.D61</td>
<td>4 %</td>
<td>3 %</td>
<td>Shortened survival</td>
<td></td>
</tr>
<tr>
<td>PHF6</td>
<td>Transcriptional regulation</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td>Mainly truncating variants and missense variants in PHD2 domain (p.R274Q and p.K235E)</td>
<td>3 %</td>
<td>2 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTPN11</td>
<td>Signal transduction</td>
<td>Exons 2, 3, 4, 7, 8, 12, and 13</td>
<td>Missense mutations</td>
<td>N-SH2 and PTP domains</td>
<td>1 %</td>
<td>1 %</td>
<td>JMML and childhood AML (both acquired or inherited) but rare in adults with MDS (1%)</td>
<td></td>
</tr>
<tr>
<td>RAD21</td>
<td>Cohesin complex</td>
<td></td>
<td>Multiple types of pathogenic variants but mainly truncating variants</td>
<td></td>
<td>2%</td>
<td>8%</td>
<td>2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&amp;2, RAD21, SMC1A and SMC3. Mutually exclusive.</td>
<td></td>
</tr>
<tr>
<td>RUNX1</td>
<td>Transcriptional regulation</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td></td>
<td>11 %</td>
<td>8 %</td>
<td>Shortened survival?. Associated with unfavorable clinical outcome.</td>
<td></td>
</tr>
<tr>
<td>SETBP1</td>
<td></td>
<td>Exon 4</td>
<td>Missense variants</td>
<td>p.S867; p.D868; p.S869; p.G870; p.S871</td>
<td>4%-9%</td>
<td></td>
<td>Associated with poor overall survival and high risk of leukemic evolution</td>
<td></td>
</tr>
<tr>
<td>SMC1A</td>
<td>Cohesin complex</td>
<td>Exons 2, 11, 16 + 17</td>
<td>Mainly missense variants</td>
<td></td>
<td>&lt;1%</td>
<td></td>
<td>&lt;1% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&amp;2, RAD21, SMC1A and SMC3. Mutually exclusive.</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Type</td>
<td>Exon(s)</td>
<td>Pathogenic variants</td>
<td>% in myeloid malignancies and % in any one of all cohesin complex genes i.e. STAG1&amp;2, RAD21, SMC1A and SMC3. Mutually exclusive.</td>
<td>Survival Impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMC3</td>
<td>Cohesin complex</td>
<td>Exons 10, 13, 19, 23, 25, 28</td>
<td>Multiple types of pathogenic variants</td>
<td>2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&amp;2, RAD21, SMC1A and SMC3. Mutually exclusive.</td>
<td>shortened survival&lt;sup&gt;111-113&lt;/sup&gt;, no impact on survival&lt;sup&gt;73&lt;/sup&gt;. Associated with poor overall survival and high risk of leukemic evolution.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRSF2</td>
<td>RNA-splicing</td>
<td>Exon 1</td>
<td>In-frame deletions and missense variants</td>
<td>18% 15%</td>
<td>shortened survival&lt;sup&gt;121,124,126&lt;/sup&gt;, no impact on survival&lt;sup&gt;73&lt;/sup&gt;.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAG2</td>
<td>Cohesin complex</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants, mainly truncating variants</td>
<td>8% 5%</td>
<td>shortened survival&lt;sup&gt;111&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2</td>
<td>DNA methylation</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants</td>
<td>36% 26%</td>
<td>no impact on survival&lt;sup&gt;8&lt;/sup&gt;, shortened survival after transplant&lt;sup&gt;8&lt;/sup&gt;, no impact on overall survival, may predict response to hypomethylating agents.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>DNA repair</td>
<td>Exons 3 to 11</td>
<td>Multiple types of pathogenic variants</td>
<td>6% 5% (17% in del(5q))</td>
<td>shortened survival&lt;sup&gt;9,73&lt;/sup&gt;, poor response after transplant&lt;sup&gt;136&lt;/sup&gt;.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U2AF1</td>
<td>RNA splicing</td>
<td>Exons 2 and 6</td>
<td>Missense variants</td>
<td>8% 6%</td>
<td>no impact on survival&lt;sup&gt;73&lt;/sup&gt;, shortened survival&lt;sup&gt;111&lt;/sup&gt;. Associated with high risk of leukemic evolution.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT1</td>
<td>DNA methylation</td>
<td>Exons 7 and 9</td>
<td>Multiple types of pathogenic variants</td>
<td>1% 1%</td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZRSR2</td>
<td>RNA splicing</td>
<td>Total coding region</td>
<td>Multiple types of pathogenic variants, mainly truncating variants</td>
<td>8% 5%</td>
<td>shortened survival&lt;sup&gt;121,124,125,145&lt;/sup&gt; in ZRSR2mut/TET2wt&lt;sup&gt;121&lt;/sup&gt;.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


117. Meggendorfer M, Bacher U, Alpermann T, et al. SETBP1 mutations occur in 9% of MDS/MPN and in 4% of MPN cases and are strongly associated with atypical CML, monosomy 7, isochromosome i(17)(q10), ASXL1 and CBL mutations. *Leukemia*. 2013;27(9):1852-1860.


