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

Nordic MDS Group

11th update, April 2023.

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Introduction

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

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News in issue 11

Major update in diagnostics section, including the novel classifications. Minor updates in all sections, including interpretation of NGS-data in diagnostic work-up, prognostic evaluation and treatment of high risk MDS

Evidence levels and recommendation grades

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

Table 1.

Levels of evidence

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

Grades of recommendation

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

Diagnostic workup of suspected MDS

The diagnosis of MDS rests largely on morphological 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 × 10^9/L, platelets <150 × 10^9/L)[1].

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 [2].

Chromosomal aberrations are detected in approximately 50 % of newly diagnosed MDS[3] and cytogenetic analysis should be performed in all cases with suspected MDS[4].

Next-generation sequencing (NGS) can detect somatic mutations in 90%(?) of MDS patients and provides important additional information. The diagnosis of MDS requires integration of all findings.

Table 2. 2017 revision of the WHO classification of adult MDS

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

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

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

[d] Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD.

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

Table 3. The 2017 revised WHO classification of myelodysplastic/myeloproliferative neoplasms in adults

Disease	Peripheral blood findings	Bone marrow findings
Chronic myelomonocytic leukemia (CMML)	Peripheral blood monocytosis > $1x10^9$/l Not meeting WHO criteria for BCR/ABL1-positive chronic myeloid leukemia (CML), primary myelofibrosis (PMF), polycythemia vera (PV) of essential thrombocythemia (ET) [1] No rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* < 20 % blasts [2] 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	Dysplasia in one or more myeloid lineage[1] < 20 % blasts [2]
Atypical chronic myeloid leukemia, *BCR-ABL1* negative (aCML)	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophils and their precursors [3]10 % of leukocytes No *BCR-ABL1* fusion gene No evidence of *PDGFRA, PDGFRB* or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia) No or minimal basophilia Monocytes < 10% of leukocytes Not meeting WHO criteria for PMF, PV or ET [4]	Hypercellular BM with granulocytic proliferation and granulocytic dysplasia with or without dysplastic erythroid and megakaryocytic lineages < 20 % blasts in PB and BM
Myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)	Anemia Persistent thrombocytosis > 450 x 10^9/L 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)(q21q26) or del(5q) [7] No preceding MPN, MDS (except MDS-RS), or other type of MDS/MPN	< 1 % blasts in PB and < 5 % blasts in BM Dyserythropoiesis in the BM with ring sideroblasts [3]15% of erythroid precursors[5]. Abnormal megakaryocytes as observed in PMF or ET
Myelodysplastic/ myeloproliferative neoplasm, unclassifiable (MDS/MPN)	Mixed MDS and MPN features No prior diagnosis of MDS or MPN No history of recent growth factor or cytotoxic therapy to explain MDS or MPN features No *BCR-ABL1* fusion gene or rearrangements of *PDGFRA* or *PDGFRB*	Mixed MDS and MPN features <20% blasts

[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 of 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 abundant light grey or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count. [3] The presence of mutations in genes often associated with CMML (e.g. *TET2, SRSF2, ASXL1, SETBP1*) in the proper clinical contest 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 thrombocythemic myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the bone marrow and/or MPN-associated mutations (in *JAK2*, *CALR* or *MPL*) tend to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of *SETBP1* and/or *ETNK1* mutations. The presence of a *CSF3R* mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of chronic neutrophilic leukemia or other myeloid neoplasm. [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.

Table 5. The 2022 revised WHO classification of myelodysplastic neoplasms in adults

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

1. [a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
2. [b]By definition, ≤25% bone marrow cellularity, age adjusted.
3. *BM* bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.
4.

Table 6. Childhood myelodysplastic neoplasms (MDS).

	Blasts
Childhood MDS with low blasts	<5% BM; <2% PB
Hypocellular	
Not otherwise specified	
Childhood MDS with increased blasts	5–19% BM; 2–19% PB

1. *BM* bone marrow, *PB* peripheral blood.

Table 7. Myelodysplastic/myeloproliferative neoplasms

Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Diagnostic criteria of chronic myelomonocytic leukaemia.

From: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Prerequisite criteria

1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.

2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]

3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]

4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]

Supporting criteria

1. Dysplasia involving ≥1 myeloid lineages.[d]

2. Acquired clonal cytogenetic or molecular abnormality.

3. Abnormal partitioning of peripheral blood monocyte subsets.[e]

Requirements for diagnosis

- Pre-requisite criteria must be present in all cases.

- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.

- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.

Subtyping criteria

- Myelodysplastic CMML (MD-CMML): WBC < 13 × 10^9/L

- Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 10^9/L

Subgrouping criteria (based on percentage of blasts and promonocytes)

CMML-1: <5% in peripheral blood and <10% in bone marrow

CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

1. [a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.
2. [b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (*JAK2, CALR* or *MPL*) tends to support MPN with monocytosis rather than CMML.
3. [c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.
4. [d]Morphologic dysplasia should be present in ≥10% of cells of a haematopoietic lineage in the bone marrow.
5. [e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

Table 8. The 2022 International Consensus Classification of Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53;*not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53,*; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB‖	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

*

Cytoses: Sustained white blood count ≥ 13 × 10^9/L, monocytosis (≥0.5 × 10^9/L and ≥10% of leukocytes) or platelets ≥450 × 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

†

***BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.**

‡

Although dysplasia is typically present in these entities, it is not required.

§

Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confirmed on 2 separate occasions also qualifies for MDS-EB.

‖

For pediatric patients (<18 y), the blast thresholds for MDS-EB are 5% to 19% in BM and 2% to 19% in PB, and the entity MDS/AML does not apply.

¶

AML-defining cytogenetics are listed in the AML section.

Table 9. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis (MDS/MPN-T-*SF3B1*)

Thrombocytosis, with platelet count ≥ 450 × 10^9/L
Anemia (threshold same as for MDS)
Blasts < 1% in blood and < 5% in bone marrow
Presence of *SF3B1* mutation (VAF > 10%), isolated or associated with abnormal cytogenetics and/or other myeloid neoplasm associated mutations
No history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3)(q21.3q26.2), or del(5q)*
No history of MPN, MDS, or other myelodysplastic/myeloproliferative neoplasm

*

In a case that otherwise meets the diagnostic criteria for myelodysplastic syndrome with del(5q).

Table 10. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, not otherwise specified (MDS/MPN-RS-T, NOS)

Thrombocytosis, with platelet count ≥ 450 × 10^9/L
Anemia associated with erythroid-lineage dysplasia, with or without multilineage dysplasia, and ≥ 15% ring sideroblasts
Blasts < 1% in blood and < 5% in bone marrow
Presence of clonality: demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s). In their absence, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features
Absence of *SF3B1* mutation; no *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3) (q21.3q26.2), or del(5q)*
No history of MPN, MDS, or other MDS/MPN

*

In a case that otherwise meets the diagnostic criteria for MDS with del(5q).

Table 11. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm, not otherwise specified (MDS/MPN, NOS)

Myeloid neoplasm with mixed myeloproliferative and myelodysplastic features, not meeting the criteria for any other MDS/MPN, MDS, MPN*
Cytopenia (thresholds same as for MDS)
Blasts < 20% of the cells in blood and bone marrow
A platelet count of ≥ 450 × 10^9/L and/or a white blood cell count of ≥ 13 × 10^9/L
Presence of clonality: demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s). If clonality cannot be determined, the findings have persisted and all other causes (eg, history of cytotoxic or growth factor therapy or other primary cause that could explain the myelodysplastic/myeloproliferative features) have been excluded.
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3)(q21.3q26.2),† or del(5q)‡

*

MPNs, in particular those in accelerated phase and/or in post–PV or post–ET myelofibrotic stage, may simulate MDS/MPN, NOS. A history of MPN and/or the presence of MPN-associated mutations (in *JAK2*, *CALR*, or *MPL*) particularly if associated with a high VAF, tend to exclude a diagnosis of MDS/MPN, NOS. The presence of hypereosinophilia would favor a diagnosis of CEL, NOS.

†

In a case that otherwise meets criteria for MDS-NOS.

‡

In a case that otherwise meets the diagnostic criteria for MDS with isolated del(5q).

Table 12. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with isochromosome (17q) [MDS/MPN with i(17q)]

Fulfills the general criteria for a diagnosis of MDS/MPN, NOS • Leukocytosis of ≥ 13 × 10^9/L • Cytopenia (thresholds same as for MDS) • Blasts < 20% of the cells in blood and bone marrow • Dysgranulopoiesis with non-segmented or Pseudo-Pelger Huët neutrophils • An i(17q), either isolated or occurring with one other additional abnormality [other than −7/del(7q)] • No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions • Absence of MPN-associated mutations (*JAK2, CALR* and *MPL*)* • No history of recent cytotoxic or growth factor therapy that could explain the MDS/MPN features

MDS/MPN with i(17q) is considered a provisional subentity of MDS/MPN, NOS.

*

Presence of MPN features in the bone marrow, and/or MPN-associated mutations (in *JAK2, CALR,* or *MPL*) suggests progression of an underlying MPN that was not diagnosed and should be excluded; conversely, in the appropriate clinical context, mutations particularly co-mutations in *SRSF2* and *SETBP1* genes further support this diagnosis.

Table 13. Diagnostic criteria for chronic myelomonocytic leukemia (CMML)

Monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC

Cytopenia (thresholds same as MDS)*
Blasts (including promonocytes) < 20% of the cells in blood and bone marrow
Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency†
In cases without evidence of clonality, monocytes ≥ 1.0 × 10^9/L and > 10% of the WBC, and increased blasts (including promonocytes),‡ or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for its diagnosis.
Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis§
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

*
A small proportion of cases may show only borderline or no cytopenia usually in early phase disease.
†
Based on International Consensus Group Conference, Vienna, 2018.[260]
‡
Increased blasts: ≥5% in the bone marrow and/or ≥2% in the peripheral blood.
§
For cases lacking bone marrow findings of CMML, a diagnosis of CMUS could be considered. If cytopenia is present, a diagnosis of CCMUS could be entertained. In these diagnostic settings, however, an alternative cause for the observed monocytosis would have to be excluded based on appropriate clinicopathologic correlations.

Table 14. Diagnostic criteria for clonal monocytosis of undetermined significance (CMUS)

Persistent monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on bone marrow examination‡
No criteria for a myeloid or other hematopoietic neoplasm are fulfilled
No reactive condition that would explain a monocytosis is detected

*
If cytopenia is present the nomenclature of CCMUS is suggested.
†
VAF threshold based on International Consensus Group Conference, Vienna, 2018.[260]
‡
Bone marrow findings of CMML include hypercellularity with myeloid predominance, often with increased monocytes and in a proportion of cases monoblasts and/or blast equivalents (ie, promonocytes) and/or dysplasia in at least 1 lineage.

Molecular somatic mutations have been identified in > 40 myeloid genes by next generation sequencing (NGS) in approximately 90 % of MDS patients[5,6]. The genes to be investigated at initial diagnosis, especially because of their negative prognostic impact, are TP53, ASXL1, RUNX1, and EZH2.
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 and therapeutic decision-making, please see Prognosis section for more information.
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 Dyserytropoietic Anemias (CDA), Telomere-associated syndromes including Congenital Dyskeratosis, Hereditary Sideroblastic Anemia, Fanconi Anemia (FA), Congenital Neutropenias (Kostmann, Schwachman-Diamond), Diamond-Blackfan Anemia (DBA), familial platelet disorders including those with *RUNX1* mutation, and *GATA2*-deficiency syndrome. 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.
- Symptoms related to cytopenia (e.g. bleeding, 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 (BM) and peripheral blood (PB) smears for the assessment of dysplasia and percentage of blasts and (presence of) ring sideroblasts together with histological examination of a BM trephine biopsy, according to the WHO 2017 classification[4]. Repeated BM 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 BM 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 BM cells (including erythroid precursors) and a 200-leukocyte differential count in PB smears.
- Marrow histology/immunohistochemistry (IHC): Evaluation of marrow sections provides additional diagnostic and prognostic information (*e.g.* cellularity, marrow fibrosis, altered marrow architecture, megakaryopoiesis, focal infiltrates), and helps to rule out other diseases presenting with cytopenia and/or dysplasia. IHC for CD34 and p53 is recommended at diagnosis and during follow-up. The presence of cells with strong nuclear p53 staining may indicate an underlying *TP53* mutation[7].

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 all MDS patients at diagnosis to further refine risk stratification and strengthen the diagnosis in borderline cases[8,9].

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

Clonal hematopoiesis is gradually more prevalent 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 carry 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)[10]. 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[11].

Table 15. Comparison of genetic characteristic between CHIP, CCUS and MDS (adapted from Bejar[10])

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

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

Differential diagnosis:
The diagnosis of MDS may be difficult, in particular in patients with less than 5 % bone marrow blasts and 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)
- Lymphoid neoplasms (e.g. Hairy cell leukemia; Myeloma)
- Other cancers infiltrating the bone marrow
- Congenital cytopenias/bone marrow failure disorders

Prognosis

IPSS for MDS (International Prognostic Scoring System)

(Greenberg et al, 1997[13]). The IPSS score is deemed obsolete and is not included in the guidelines anymore.

Revised IPSS (IPSS-R)

(Greenberg et al., 2012[14]. Based on 7012 untreated patients excluded s/t-MDS and CMML with leukocyte count >12 x10^9/l. Follow this link to perform online IPSS-R scoring: IPSS-R

Table 17. IPSS-R prognostic groups and score values

Prognostic subgroup (%)	Cytogenetic abnormalities	Median Survival (y)	Median AML evolution, 25%, y
Very good (4%/3%)	-Y, del(11q)	5.4	NR
Good (72%66%)	Normal, del(5q), del(12p), del(20q), double incl. del(5q)	4.8	9.4
Intermediate (13%/19%)	der(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor (4%/5%)	-7, inv(3)/t(3q)/del(3q), double incl. -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very poor (7%/7%)	Complex: > 3 abnormalities	0.7	0.7

Prognostic variable	Score						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blasts, %	≤ 2	-	> 2 - < 5	-	5 - 10	> 10	-
Hemoglobin	≥ 100	-	80 - < 100	< 80			
Platelets	≥ 100	50 - < 100	< 50				
ANC	≥ 0.8	< 0.8					

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

Molecular IPSS (IPSS-M)

(Bernard et al, 2022, DOI:https://doi.org/10.1056/EVIDoa2200008)(link International Working Group for the Prognosis of MDS (IWG-PM) | MDS Foundation (mds-foundation.org).)

The IPSS-M score is based on diagnostic variables including clinical parameters (hemoglobine, platelets, bone marrow blasts), IPSS-R cytogenetic categories and additionnal molecular markers from NGS analysis. The IPSS-M is validated in MDS and MDS/MPN with white blood cells count < 13x109/l and in s/t-MDS. IPSS-M score led to the restratification of 46% of patients from the IPSS-R categories. Of those, 74% were restratified in higher risk IPSS-M categories while 26% were reclassified in lower risk categories. For detailed information about how the IPSS-M score is built, see appendix nr XX. The IPSS-M is not yet validated for use in dynamic settings.

Distribution of patients across continuous IPSS-M scores and IPSS-M categories

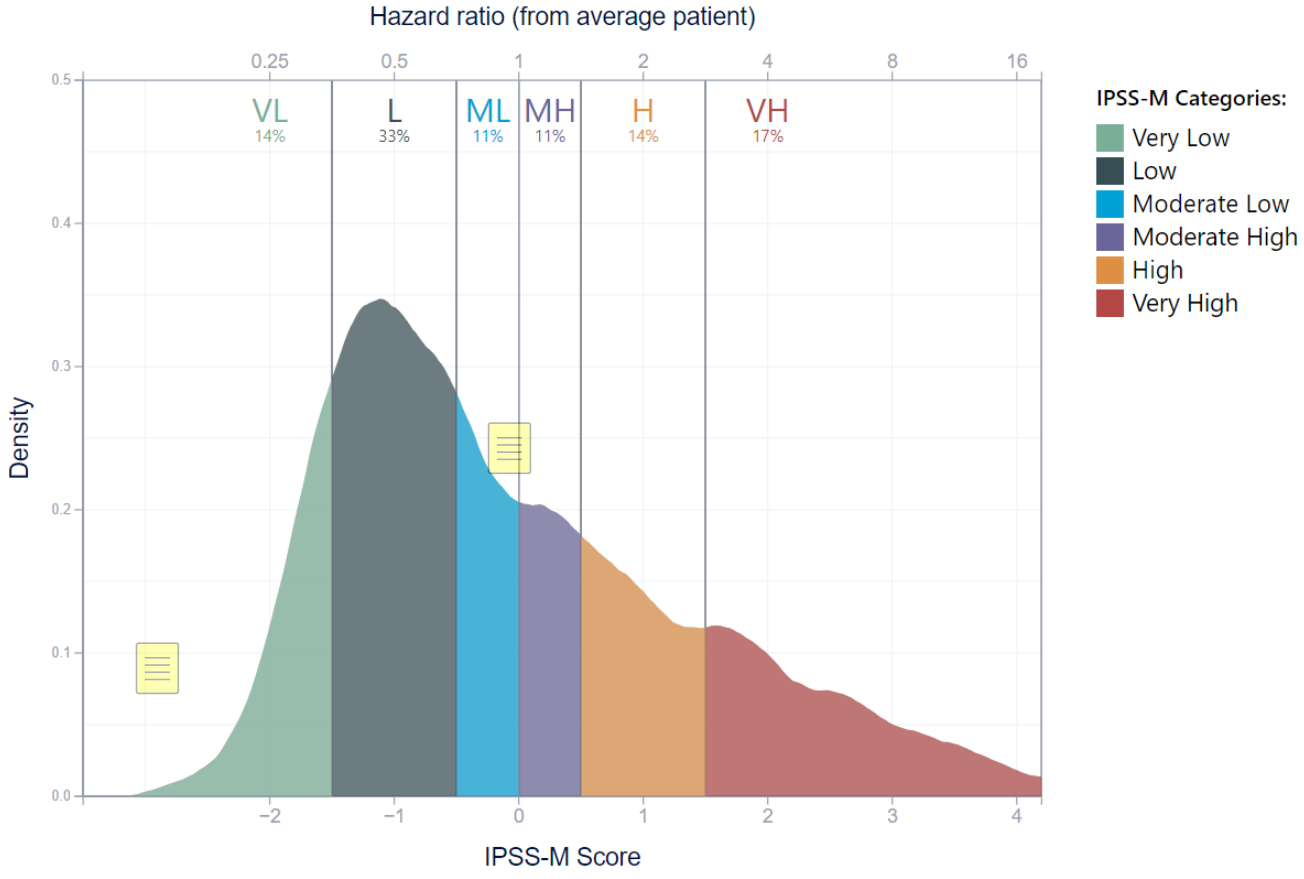

Table – **Overall survival and leukemia-free survival per IPSS-M risk category** https://doi.org/10.1056/EVIDoa2200008)

Table 2. Summary of Clinical Outcomes for 2701 Patients by IPSS-M Risk Category.*

Characteristic	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients — No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39–0.67)	1.0 (Reference)	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS (25–75% range) — yr‡	9.7 (5.0–17.4)	5.9 (2.6–12.0)	4.5 (1.6–6.9)	2.3 (0.91–4.7)	1.5 (0.80–2.8)	0.76 (0.33–1.5)
Median OS (25–75% range) — yr	10.6 (5.1–17.4)	6.0 (3.0–12.8)	4.6 (2.0–7.4)	2.8 (1.2–5.5)	1.7 (1.0–3.4)	1.0 (0.5–1.8)
AML-t — %						
By 1 yr	0.0	1.7	4.9	9.5	14.3	28.2
By 2 yr	1.2	3.4	8.8	14.0	21.2	38.6
By 4 yr	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML — %						
By 1 yr	2.2	8.5	12.0	18.0	19.3	30.6
By 2 yr	7.0	16.2	19.8	31.1	39.8	45.6
By 4 yr	15.9	29.5	33.6	51.1	54.2	51.3

* Key metrics are presented across clinical end points per IPSS-M risk category. AML denotes acute myeloid leukemia; AML-t, acute myeloid leukemia transformation; CI, confidence interval; IPSS-M, International Prognostic Scoring System with Molecular; LFS, leukemia-free survival; and OS, overall survival.

† Hazard ratio is for the risk of leukemic transformation or death. Because the low category had the largest size, it was used as the reference level.

‡ The 25 to 75% range represents the central interquartile interval. For example, for a 25 to 75% OS range from A to B years, 50% of patients lived longer than A years and died before B years.

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

In daily clinical practice and for inclusion in clinical studies simplified risk categories are often used.

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 are of particular value for categorization of IPSS-R intermediate risk patients.

Yet, there are no widely accepted simplified categories for IPSS-M. Estimated outcomes for very-high and high risk IPSS-M categories and for very-low and low risk IPSS-M categories are constitent with higher risk and lower risk disease, respectively. In cases classified as moderate-low or moderate-high risk IPSS-M the individual IPSS-M score as well as additional predictive markers (comorbidities, fibrosis, disease evolution) should be taken into consideration for treatment decision making.

Additional prognostic factors

- MDS-specific comorbidity index (MDS-CI)[15] is based on: cardiac, liver, renal, pulmonary disease and solid tumors
- Bone marrow fibrosis grade 2 and 3 confers an inferior prognosis[16-18]
- Dynamics of the disease (progressive disease e.g. increase of bone marrow blast percentage, progression of cytopenia, clonal evolution)

Impact of mutated genes on phenotype and prognosis

- Several mutations are reported to be associated with poor prognosis *TP53, EZH2, ETV6, RUNX1, NRAS* and *ASXL1*[5,6,9]
- *TP53* and RAS pathway mutations (*NRAS, KRAS, PTPN11, CBL, NF1, RIT1, FLT3,* and *KIT*) associated with high relapse risk after transplantation[19]
- The allelic status of *TP53* mutation is reported to be an important predictor of prognosis and treatment response in MDS. It seems that multiple hits *TP53* mutation state only is associated with complex karyotype and appears to be a predictor of transformation to AML and death independently of IPSS-R score. However, outcomes in patients with monoallelic *TP53* mutation are similar to those with wild-type TP53. In both *de novo* and t-MDS, patients with multiple hits *TP53* mutation state seem to have significantly worse outcomes after therapies than patients with mono-allelic *TP53* mutation[20]
- DDX41 can appear both as inherited or acquired variants and are reported to be associated with a favourable outcome[21,22]
- *SF3B1*mutation is associated with ring sideroblasts and a trend towards longer survival[23]
- Number of pathogenic variants in a patient has been found to be prognostically significant[6,9,24,25].

Recommendation for diagnosis and prognosis

- All patients should be classified according to WHO 2017 classification.
- All patients should be risk stratified according to IPSS-R and IPSS-M.
- Additional prognostic features, such as bone marrow fibrosis, co-morbidity
- MDS should be reported to the National Cancer registries in all Nordic countries and to MDS specific registries, if applicable.
- NGS panel should be performed in all MDS patients at diagnosis and gives valuable information for diagnostic classification

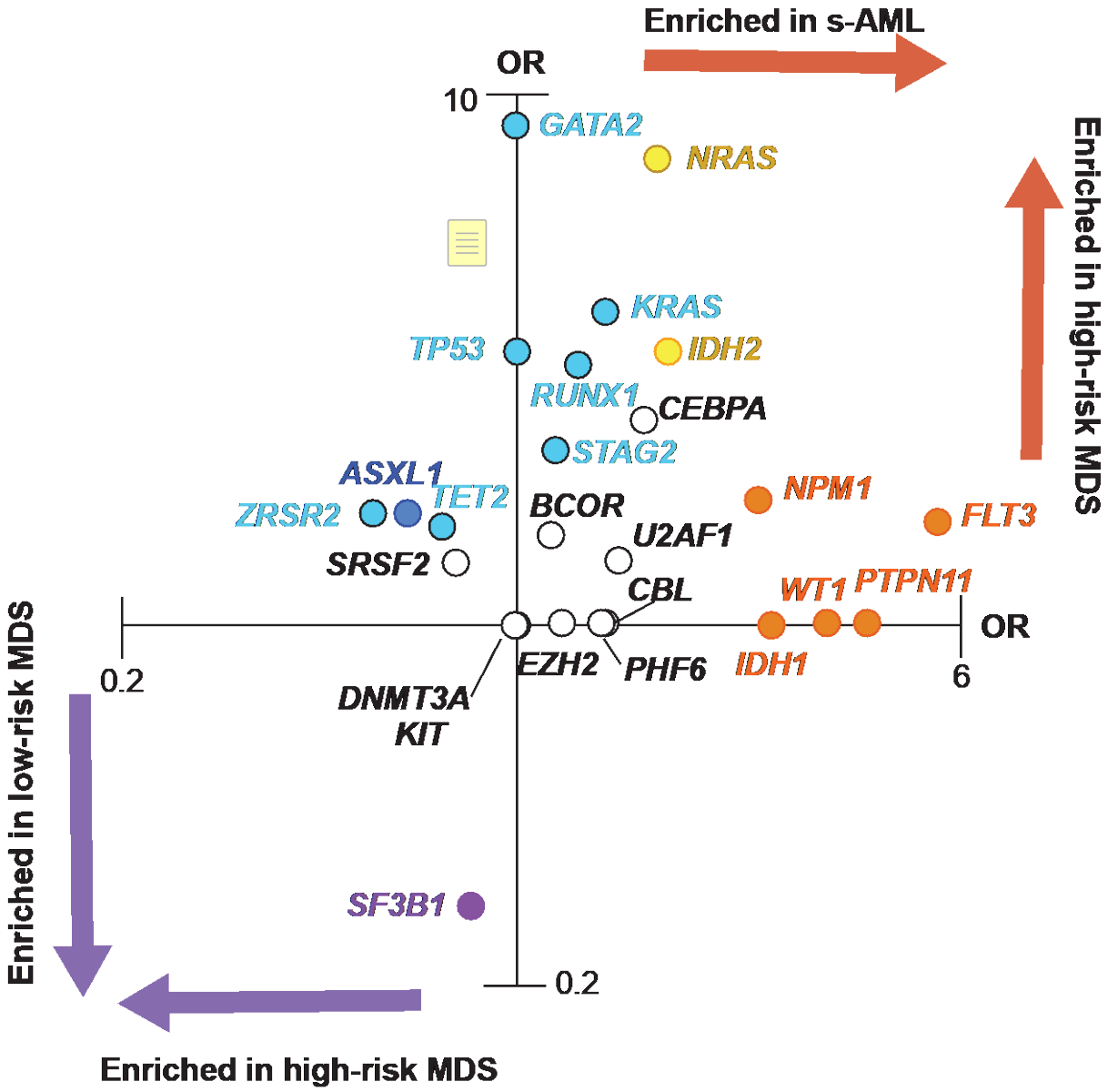

Figure 1. Enrichment of mutations in sAML and high risk MDS versus high-risk and low-risk MDS respectively. Enrichment of mutations expressed as odds ratio (OR) of mutation rates in s-AML vs high risk MDS (x-axis) and in high risk MDS vs low risk MDS (y-axis). Non-significant OR are represented by black circles. Adapted from [26].

International Working Group (IWG) modified response criteria

The IWG criteria[27] 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[28].

Table 18. Proposed modified IWG response criteria for altering natural history of MDS

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

Proposed modified IWG response criteria for haematological improvement

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

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). 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. High-quality transfusion- and chelation therapy, when indicated.
4. Evaluate patients with MDS with single lineage dysplasia (MDS-SLD) and MDS with multiple lineage dysplasia (MDS-MLD) for immunosuppressive treatment.
5. Lenalidomide treatment for patients with IPSS-R low and intermediate risk MDS with isolated del(5q), who have failed growth factor treatment or are not eligible for this treatment according to the predictive model, and who are not p53 positive by immunohistochemistry. Extreme precaution with lenalidomide treatment in younger patients who may be eligible for allogeneic SCT.
6. Patients with severe cytopenia and/or transfusion dependency who have failed other relevant therapies should be considered for experimental treatment within a clinical trial.

Algorithm for treatment of patients with high-risk MDS

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

Supportive Care

Transfusion

A recent study suggests that quality of life is improved with higher target Hb levels for transfusion[29]. 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 i.v. or s.c. infusion, and Deferasirox and Deferiprone, both given orally, the latter only available in some Nordic countries. Two large prospective phase 2 trials have been conducted, in one trial 341 patients with MDS were treated with deferasirox for one year[30]. In the recent published Telesto trial 225 patients were randomised 2 to 1[31]. In both studies, 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. In the Telesto trial median EFS was prolonged by 0.9 y (3.9 years in the treatment arm versus 3 years in the placebo arm). There exist no studies proving evidence for a beneficial 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 potential candidates for allogeneic transplantation in the future 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
- 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. The start dose is 7-14 mg/kg with a target dose of 14-28 mg/kg.
- 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 immune 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[32] 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[33]. 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-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 19. Predictive score for response to erythropoiesis stimulating agents

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

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

Response criteria for evaluation of erythroid response

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

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

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

Dosing of erythropoiesis stimulating agents

- **Induction phase:**

- **EPO:** Start with EPO 30 000 U/week (reduce initial dose if impaired renal function or low body weight). Increase to 30 000 twice weekly if no response after 8 weeks. Doses higher than 60 000 U/week are not recommended .
- **DAR:** Start with 300 µg/14 days or 150 µg/week (reduce initial dose if impaired renal function or low body weight). Increase to 300 µg/week if no response after 8 weeks.
  - Aviod starting with 300 µg/week, since this may result in a rapid increase in Hb-level to supra normal levels for a period of time due to the extended half-life of DAR. Supra normal Hb-level is associated with increased risk of thrombosis.
- **G-CSF:** Add if no response to 8 weeks of full dose EPO or DAR. Start with 300 µg (or equivalent) once weekly, alternatively 120 µg 2-3 times a week. Aim at a clear rise in neutrophil count (to 6-10 x 10^9/l). Maximum dose 300 µg x 3 times a week.
  - Long-acting G-CSF has not been evaluated in MDS and cannot be recommended.
- **Target hemoglobin level <120 g/l**
- **Overdose**: If Hb-levels increase above 130 g/l then interrupt treatment and resume treatment at a lower dose when Hb falls below 120 g/l. If Hb-levels increase above the upper normal level, then stop growth factors and consider vensectio; restart 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.

Luspatercept for lower-risk MDS with ring sideroblasts

Background

Luspatercept received a positive evaluation from EMA in july 2020. It is indicated for the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk MDS with ring sideroblasts who were ineligible for or lacked response to erytropoiesis stimulating agents[34]. Luspatercept is given as a sc injection og 1.0 mg/kg every 3rd week. The dose can be increased to 1.33 mg/kg if the patient is not transfusion independent after 2 consecutive doses, and can be increased to 1.75 mg/kg if the patient still requires transfusions after 2 consecutive injections.

Reimbursement for MDS-patients is still not possible in many Nordic countries.

Recommendation luspatercept
Recommendation grade A, evidence level Ib.

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[35] 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[35].

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

- 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[36].

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 to selected transplant-eligible patients it should only be in the absence of p53 alterations, with careful monitoring for signs of disease progressions.
- 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 hematopoietic cell transplantation (allo-HCT) in MDS

Background

Allogeneic hematopoietic cell transplantation (allo-HCT) is the only known curative treatment option in patients with MDS[37]. The outcome after allo-HCT is very heterogeneous and prognosis has been delineated by different clinical scores such as the Revised International Scoring System (IPSS-R)[38]. Five years overall survival (OS) ranges from 23 % to 71 % for patients with very high-risk and very low risk IPSS-R scores, respectively[38]. Additional prognostic factors include age, HCT specific comorbidity index (HCT-CI)[39], donor HLA match, sex match, therapy-related MDS and response to induction chemotherapy[40-42]. Fibrotic bone marrow pathology is also associated with a poor prognosis[43]. Complex or monosomal karyotype are predictive of a poor outcome, and several studies have shown a poor prognosis related to genetic mutations, particularly TP53[19,44]. Relapse is the most significant cause of death with an overall relapse rate (RR) about 30 %. The overall non-relapse mortality (NRM) has been reported to be 5-20 %. Increasing intensity of conditioning reduces the risk of relapse but increases the risk of NRM according to several retrospective studies[45,46] and few randomized studies comparing myeloablative (MAC) regimens with reduced intensity conditionings (RIC)[47,48]. Results have improved during the last decade despite more elderly patients have been possible to transplant due to the introduction of RIC and reduced toxicity conditioning (RTC) along with better matched unrelated donors and supportive care[49]. Promising results have been described with the RTC-regimen Treosulfan-Fludarabine (Treo-Flu) with a reduced RR compared to standard RIC without a corresponding higher NRM compared to conventional MAC[49-52]. In a randomized study Treo-Flu has been shown to have a survival advantage compared to RIC Flu/Bu[50].

Indications (sibling or unrelated donor)

- 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 also 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 allo-HCT.

Cytoreductive chemotherapy prior to allo-HCT

"Debulking" treatment prior to transplantation with RIC or MAC has not been shown to yield improved outcomes in retrospective studies[53,54]. In particular, unsuccessful treatment is a predicter of relapse (treated but not in complete remission at time of transplantation)[42].
However, some studies have found that the percentage of blasts at the time of transplantation has an impact on prognosis[55]. Cytoreductive therapy is therefore often given before allo-HCT, but the value is not established due to lack of randomized trials and conclusive retrospective data. 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 $\geq$ 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[56], 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/) [56]. 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 20. HCT-CI

Comorbidity	*Definition of comorbidity*	*HCT-CI weighted score*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, § congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL (178 mmol/l), on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV$_1$ 66%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV$_1$≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

SUM	__

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

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

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

Azacitidine

Background

Azacitidine is approved for treatment of IPSS INT-2 and HR MDS and MDS/AML with 20-30 % blasts in patients not eligible for hematopoietic stem cell transplantation. 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[57]. 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)[57-63]. 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[58,64]. 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)[57,64,65].
Two publications suggest that azacitidine treatment as a bridging therapy to allogeneic SCT is feasible and does not seem to alter the post-transplant prognosis[66,67].
Based on these findings, azacitidine is generally recommended as first choice for HR-MDS and MDS/AML (with 20-30 % blasts) unless the patient is young with good prognostic features for response to AML-like chemotherapy.

Decision making and treatment

Indication

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

- MDS IPSS INT-2 and High (in rare instances in INT-1 with severe cytopenias, where all other potential treatment modalities have failed).
- MDS/AML with 20-30 % blasts.
- Expected survival exceeding 3 months.

Azacitidine treatment

- Azacitidine 75 mg/m^2 sc d 1-7 repeated every 28 days. (Alternative dosing schedules can be considered: 100 mg/m^2 sc d 1-5 or 75 mg/m^2 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 unnecessary 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[68-74]. Only few studies were randomized, and then often with the purpose to study the effect of G-CSF or GM-CSF in combination with chemotherapy. All studies taken together showed a median complete remission (CR) rate of 43 % (range: 18-74 %), and overall survival (OS) varying between 6-21 months. Between 8-27 % of the patients died within the first month of treatment. Patients with normal LDH and/or WBC < 4 x 10^9/l and absence of poor risk cytogenetics had better CR rates. In some studies, duration of antecedent MDS was inversely related to achievement of CR. CR durations are generally short and there is no evidence, that AML like chemotherapy alters the natural history of MDS, i.e. overall survival is not affected by the treatment. There are no data to support that high dose chemotherapy with autologous stem cell support is superior to AML like chemotherapy[75,76]. 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.

Melphalan

Three small phase 2 studies in high-risk MDS patients report a response rate of up to 30 % in selected patients, i.e. improved blood cell counts and reduced/abolished transfusion need. The toxicity was mild[77-79].

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

Recommendation
Recommendation grade B, evidence level IIb.

Low-dose cytosine arabinoside

One large randomized study comparing low dose cytosine arabinoside (LDAC) and supportive care in predominantly high-risk MDS patients showed a response rate of approximately 30 % in the LDAC arm, but no benefit in terms of overall survival and transformation to AML[80-82]. Fatal hematological toxicity at a frequency of up to 19 % was reported for LDAC. Ara-C has in a subgroup analysis of the Aza 001 trial been shown to be inferior to azacitidine[57].

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

Recommendation
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.

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 [6,83].
According to European Hematology Association guidelines, NGS analysis is recommended for all CMML patients being considered for active treatment [84]. Mutations in ASXL1, RUNX1, NRAS and SETBP1 have demonstrated independent prognostic value, leading to their inclusion in the CPSS-mol [85], an update to the CPSS [86]. ASXL1 mutation have a poor prognostic effect in several cohorts and is included in the Groupe Francophone des Myelodysplasies (GFM) prognostic model and the Mayo Molecular Model (MMM) [84,87]. TET2 mutation in patients with wildtype ASXL1 may be associated with a favorable prognosis [88]. European guidelines recommend risk assessment in CMML using any of these scores: the CPSS-mol, GFM or MMM if mutation status is available, and the CPSS or MD Anderson Prognostic Scoring System (MDAPS) [89] if it is not [84].

CMML specific scoring system (CPSS) [86] 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 21. CPSS score

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

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

Table 22. CMML genetic score and CPSS-Mol (Elena et al[85])

Variables and prognostic score values of the CMML genetic score

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

Cytogenetic risk groups are defined according to Such et al[86]: low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

Variables and prognostic score values of the CPSS-Mol

	Genetic risk group	**BM blasts**	**WBC count**	**RBC transfusion dependence**
Variable score				
0	Low	< 5 %	< 13x10^9/L	No
1	Intermediate-1	≥ 5 %	≥ 13x10^9/L	Yes
2	Intermediate-2	Na	Na	Na
3	High	Na	Na	Na
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[90] and Such et al.[86]

The CPSS-mol score 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) [85]. The learning and validation cohorts consisted of 214 and 260 CMML patients, respectively [85].

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

Allogeneic hematopoietic cell transplantation (allo-HCT) in CMML

Chronic myelomonocytic leukemia is a challenging disease being difficult to cure even with allo-HCT [91]. Non-relapse mortality (NRM) occurs in 20-40% of CMML patients within 5 years of allo-HCT, and relapse in 30-50%, resulting in overall survival of approximately 30-40% [49,92-94]. The significance of factors such as patient age and sex are uncertain, and no significant effect on transplantation outcomes has been demonstrated for conditioning intensity, stem cell source, or donor type (unrelated vs. related). The CMML-specific Prognostic Scoring System (CPSS) [86] has also been applied in the context of allo- HCT [92]. A high CPSS score was associated with a poor overall survival, specifically because of a higher risk of death after the occurrence of relapse [92]. Complete remission (CR) at the time of transplantation has been associated with a favorable overall survival but had not been shown to have an effect on relapse rate [94]. Development of chronic graft

versus host disease (GVHD) after transplantation heralds a favorable prognosis, highlighting the importance of the coexisting graft versus leukemia effect [93].

CPSS mol incorporates mutations in *RUNX1, NRAS, ASXL1* and *SETBP* in the prognostic system (Table 11). However, the impact of mutational status on outcome after allogeneic HCT in CMML has only been sparsely investigated [44,95]. It has been found that patients with mutations in RAS pathways have a poor prognosis, that do not appear to be overcome by allo-HCT. Thus other strategies than transplantation should be considered – especially for fragile and elderly patients.

Indications for Allo-HCT

- Fit patients without severe comorbidities CMML-2 or CMML-1 with at least CPSSmol 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 or at least < 10 % blasts.
- For more information see the section of Allo-HCT for MDS.

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 and for treatment of AML in combination with hypomethylating drugs. Retrospective data showed overall response rate of 59 % in a cohort consisting of both treatment-naïve and relapsed/refractory MDS patients receiving venetoclax and hypomethylating drugs [96].

Preliminary data from a single arm phase 1b study for treatment-naïve HR-MDS patients (NCT02942290) demonstrated manageable safety and a combined complete remission / marrow complete remission rate of 79 %.

The combination of hypomethylating agents and venetoclax 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, with myelosuppression and febrile neutropenia and pneumonia as common serious adverse events.

Responses are seen earlier than for azacitidine alone, in general after 1-2 cycles. Dose reduction of both azacitidine and venetoclax should be considered if signs of severe myelosuppression.

The clinical experience from the Nordic countries is mainly from transplantation-candidates where the drug has been used as bridging therapy[97].

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/m^2 by iv infusion over 3 hours every 8 hours, d 1-3 repeated every 6 weeks. Alternatively give 20 mg/m^2, 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/m^2) on days 1 through 10 of 28-day cycles according to Welch *et al*[98] 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

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AB: NA
JC: NA
LC: NA
MC: NA
ID: NA
EE: NA
LF: NA
HG: NA
AG: NA
KG:
JWH: NA
MSH: NA
MJ: NA
LK: NA
EHL:
PL:
MM: Honoraria from Celgene and Sanofi
JMN: NA
LN: NA
AP: NA
EP: NA
KRJ: NA
LS: NA

JU: NA

Table 23. Genes frequently mutated in MDS.

Gene	Function	Target regions	Types of pathogenic variants	Main hotspots	Mutational frequency[5]	Mutational frequency[6]	Comment	Ref.
ASXL1	Chromatin modification	Exon 13	Nonsense and frame-shift variants	p.E635fs*; p.G646fs	23 %	14 %	Shortened survival[9,99,100]. Associated with unfavorable clinical outcome in all myeloid neoplasms (MDS, MDS/MPN, MPN).	9,99-104
BCOR	Transcriptional regulation	Total coding region	Nonsense and frame-shift variants		4 %	5 %	Shortened survival[105]. Frequent in aplastic anemia[106].	105-107
CALR	Signal transduction	Exon 9	Indels in exon 9	p.L367fs*46; p.K385fs*47			MPN	
CSFR3	Signal transduction	Exon 14 and 17	Missense (E14) and truncating (E17) variants	p.T618I			Strictly associated with CNL, found in a subset of patients with aCML.	108-111
CBL	Signal transduction	Exon 8 and 9	Multiple types of pathogenic variants		5 %	4 %	Shortened survival[9].	9,112-116
DDX41	RNA-helicase; RNA splicing and RNA processing	Total coding region	Multiple types of pathogenic variants	p.R525	2,4 % [22]		A subset of cases with inherited mutations in *DDX41* can have biallelic DDX41 mutation, with one mutation being germline.	21,22,117
DNMT3A	DNA methylation	Exon 7 to 23	Multiple types of pathogenic variants mainly missense	p.R882	13 %	11 %	Shortened survival[118].	8,118
ETNK1	Ethanolamine phosphorylation, mitochondrial function		Missense mutations	p.H243Y; p.N244S	3-9 % [119]		aCML and CMML	119-121
ETV6	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants	PNT and ETS domains	2 %	1 %	Shortened survival[9].	9,122,123
EZH2	Chromatin modification	Total coding region	Multiple types of pathogenic variants	SET-domain (p.R690)	6 %	5 %	Shortened survival[9,99].	9,99,124,125

GATA1	Transcriptional regulation	Exon 2	Multiple types of pathogenic variants				AML in Down syndrome	
GATA2	Transcriptional regulation	Exon 2 to 6	Multiple types of pathogenic variants	exon 5 and 6 (ZF1 and ZF2 domains)			Familial AML/MDS.	126-130
IDH1	DNA methylation	Exon 4	Missense variants	p.R132	3 %	3 %	Shortened survival[131].	131-133
IDH2	DNA methylation	Exon 4	Missense variants	p.R140; pR172	4 %	4 %		131,132,134,135
JAK2	Signal transduction	Exon 14 and 12	V617F (E14) and in-frame del/ins or missense variants in (E12)	p.V617F	5 %	5 %	No impact on survival[9,99].	9,99
KIT	Signal transduction	Exons 8-14, Exon 17	Multiple types of pathogenic variants	p.D816	1 %	2 %	AML	
KRAS	Signal Transduction	Exon 2 and 3	Missense variants	p.D12, p.D13, p.D61	3 %	2 %		
MPL	Signal transduction	Exon 10	Missense variant	p.W515L	3 %	2 %	MPN	
NF1	Signal transduction	Total coding region	Multiple types of pathogenic variants		3 %	4 %	Familial cases, JMML	136
NPM1	Signal transduction	Exon 12	Insertions	p.W288fs*12	1 %	1 %	AML	
NRAS	Signal Transduction	Exon 2 and 3	Missense variants	p.D12, p.D13,p.D61	4 %	3 %	Shortened survival	9
PHF6	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants	Mainly truncating variants and missense variants in PHD2 domain (p.R274Q and p.K235E)	3 %	2 %		137
PPM1D	DNA damage response	Total coding region	Nonsense or frameshift mutations in the sith exon creating a C-terminal truncated protein	Mainly truncating variants in the C-terminal domain			Enriched in t-AML and t-MDS but also in clonal hematopoiesis	138,139
PTPN11	Signal transduction	Exons 2, 3, 4, 7, 8, 12, and 13	Missense mutations	N-SH2 and PTP domains	1 %	1 %	JMML and childhood AML (both acquired or inherited) but rare in adults with MDS (1%)	140-142

RAD21	Cohesin complex		Multiple types of pathogenic variants but mainly truncating variants				2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	143-145
RUNX1	Transcriptional regulation	Total coding region	Multiple types of pathogenic variants		11 %	8 %	Shortened survival[9]. Associated with unfavorable clinical outcome.	9,99,103
SETBP1		Exon 4	Missense variants	p.S867;p.D868; p.S869; p.G870; p.I871	4%-9%		Associated with poor overall survival and high risk of leukaemic evolution	104,146-150
SF3B1	RNA splicing	Exons 11 to 16	Missense variants	p.K700; p.K666; p.H662;p.H662;p.R625; pE622	33 %	25 %	Longer survival[151]. No impact on survival[99,152]. Associated with good overall survival and low risk of leukemic evolution.	148,153-157
SMC1A	Cohesin complex	Exons 2, 11, 16 + 17	Mainly missense variants				<1% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	143-145
SMC3	Cohesin complex	Exons 10, 13, 19, 23, 25 + 28	Multiple types of pathogenic variants				2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive.	143-145
SRSF2	RNA-splicing	Exon 1	In-frame deletions and missense variants	p.P95_R102del; p.P95	18 %	15 %	Shortened survival[153,156,158]. No impact on survival[99]. Associated with poor overall survival and high risk of leukaemic evolution.	153,154,156-165
STAG2	Cohesin complex	Total coding region	Multiple types of pathogenic variants, mainly truncating variants		8 %	5 %	2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. Shortened survival	145
TET2	DNA methylation	Total coding region	Multiple types of pathogenic variants		36 %	26 %	No impact on survival[9,99,166]. Shortened survival after transplant[8]. No impact on overall survival, may predict response to hypomethylating agents.	59,166-172
TP53	DNA repair	Exon 3 to 11	Multiple types of pathogenic variants		6 %	5% (17% in del(5q))	Shortened survival[9,99] after transplant[168]. Poor response	9,99,103,168,173,174
U2AF1	RNA splicing	Exon 2 and 6	Missense variants	p.S34; p.R156; p.Q157	8 %	6 %	No impact on survival[99]. Shortened surviva[148]l. Associated with high risk of leukemic evolution.	153,156,164,175,176

WT1	DNA methylation	Exon 7 and 9	Multiple types of pathogenic variants	1 %	1 %	AML	
ZRSR2	RNA splicing	Total coding region	Multiple types of pathogenic variants, mainly truncating variants.	8 %	5 %	No impact on survival[156]. Shortened survival in ZRSR2mut/TET2wt.[153]	[153,156,157,177]

Table 24. Genes frequently mutated in MDS.

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CALR	Signal transduction	Exon 9	Indels in exon 9	p.L367fs*46; p.K385fs*47			MPN	
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STAG2	Cohesin complex	Total coding region	Multiple types of pathogenic variants, mainly truncating variants		8 %	5 %	2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. Shortened survival	[145]

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ZRSR2	RNA splicing	Total coding region	Multiple types of pathogenic variants, mainly truncating variants.		8 %	5 %	No impact on survival[156]. Shortened survival in ZRSR2mut/TET2wt.[153]	153,156,157,177

References

1. Greenberg PL, Tuechler H, Schanz J, et al. Cytopenia levels for aiding establishment of the diagnosis of myelodysplastic syndromes. *Blood*. 2016;128(16):2096-2097.
2. Westers TM, Ireland R, Kern W, et al. Standardization of flow cytometry in myelodysplastic syndromes: a report from an international consortium and the European LeukemiaNet Working Group. *Leukemia*. 2012;26(7):1730-1741.
3. Haase D. Cytogenetic features in myelodysplastic syndromes. *Ann Hematol*. 2008;87(7):515-526.
4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
5. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. 2014;28(2):241-247.
6. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122(22):3616-3627; quiz 3699.
7. Jadersten M, Saft L, Pellagatti A, et al. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. *Haematologica*. 2009;94(12):1762-1766.
8. Bejar R. Clinical and genetic predictors of prognosis in myelodysplastic syndromes. *Haematologica*. 2014;99(6):956-964.
9. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. 2011;364(26):2496-2506.
10. Bejar R. Implications of molecular genetic diversity in myelodysplastic syndromes. *Curr Opin Hematol*. 2017;24(2):73-78.
11. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood*. 2017;129(25):3371-3378.
12. Heuser M, Thol F, Ganser A. Clonal Hematopoiesis of Indeterminate Potential. *Dtsch Arztebl Int*. 2016;113(18):317-322.
13. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079-2088.
14. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.
15. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica*. 2011;96(3):441-449.
16. Ramos F, Robledo C, Izquierdo-Garcia FM, et al. Bone marrow fibrosis in myelodysplastic syndromes: a prospective evaluation including mutational analysis. *Oncotarget*. 2016;7(21):30492-30503.
17. Buesche G, Teoman H, Wilczak W, et al. Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. *Leukemia*. 2008;22(2):313-322.
18. Della Porta MG, Malcovati L, Boveri E, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. *J Clin Oncol*. 2009;27(5):754-762.
19. Lindsley RC, Saber W, Mar BG, et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. *N Engl J Med*. 2017;376(6):536-547.

20. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26(10):1549-1556.
21. Quesada AE, Routbort MJ, DiNardo CD, et al. DDX41 mutations in myeloid neoplasms are associated with male gender, TP53 mutations and high-risk disease. *Am J Hematol*. 2019;94(7):757-766.
22. Sebert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. *Blood*. 2019;134(17):1441-1444.
23. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood*. 2015;126(2):233-241.
24. Malcovati L, Papaemmanuil E, Ambaglio I, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. *Blood*. 2014;124(9):1513-1521.
25. Karimi M, Nilsson C, Dimitriou M, et al. High-throughput mutational screening adds clinically important information in myelodysplastic syndromes and secondary or therapy-related acute myeloid leukemia. *Haematologica*. 2015;100(6):e223-225.
26. Makishima H, Yoshizato T, Yoshida K, et al. Dynamics of clonal evolution in myelodysplastic syndromes. *Nat Genet*. 2017;49(2):204-212.
27. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425.
28. Platzbecker U, Fenaux P, Ades L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;133(10):1020-1030.
29. Nilsson-Ehle H, Birgegard G, Samuelsson J, et al. Quality of life, physical function and MRI T2* in elderly low-risk MDS patients treated to a haemoglobin level of >/=120 g/L with darbepoetin alfa +/- filgrastim or erythrocyte transfusions. *Eur J Haematol*. 2011;87(3):244-252.
30. Gattermann N, Finelli C, Porta MD, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. *Leuk Res*. 2010;34(9):1143-1150.
31. Angelucci E, Li J, Greenberg P, et al. Iron Chelation in Transfusion-Dependent Patients With Low- to Intermediate-1-Risk Myelodysplastic Syndromes: A Randomized Trial. *Ann Intern Med*. 2020;172(8):513-522.
32. Desborough M, Estcourt LJ, Chaimani A, et al. Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with thrombocytopenia due to chronic bone marrow failure: a network meta-analysis and systematic review. *Cochrane Database Syst Rev*. 2016;2016(1).
33. Garelius HK, Johnston WT, Smith AG, et al. Erythropoiesis-stimulating agents significantly delay the onset of a regular transfusion need in nontransfused patients with lower-risk myelodysplastic syndrome. *J Intern Med*. 2016.
34. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *N Engl J Med*. 2020;382(2):140-151.
35. Haider M, Al Ali N, Padron E, et al. Immunosuppressive Therapy: Exploring an Underutilized Treatment Option for Myelodysplastic Syndrome. *Clin Lymphoma Myeloma Leuk*. 2016;16 Suppl:S44-48.
36. Saft L, Karimi M, Ghaderi M, et al. p53 protein expression independently predicts outcome in patients with lower-risk myelodysplastic syndromes with del(5q). *Haematologica*. 2014;99(6):1041-1049.

37. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129(13):1753-1762.
38. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. *Blood*. 2014;123(15):2333-2342.
39. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.
40. Ayuk F, Beelen DW, Bornhauser M, et al. Relative Impact of HLA Matching and Non-HLA Donor Characteristics on Outcomes of Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndrome. *Biol Blood Marrow Transplant*. 2018;24(12):2558-2567.
41. Gagelmann N, Eikema DJ, Stelljes M, et al. Optimized EBMT transplant-specific risk score in myelodysplastic syndromes after allogeneic stem-cell transplantation. *Haematologica*. 2019;104(5):929-936.
42. Heuser M, Gabdoulline R, Loffeld P, et al. Individual outcome prediction for myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia from MDS after allogeneic hematopoietic cell transplantation. *Ann Hematol*. 2017;96(8):1361-1372.
43. Kroger N, Zabelina T, van Biezen A, et al. Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis. *Haematologica*. 2011;96(2):291-297.
44. Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. *Blood*. 2017;129(17):2347-2358.
45. Luger SM, Ringden O, Zhang MJ, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplant*. 2012;47(2):203-211.
46. Martino R, de Wreede L, Fiocco M, et al. Comparison of conditioning regimens of various intensities for allogeneic hematopoietic SCT using HLA-identical sibling donors in AML and MDS with <10% BM blasts: a report from EBMT. *Bone Marrow Transplant*. 2013;48(6):761-770.
47. Kroger N, Iacobelli S, Franke GN, et al. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial). *J Clin Oncol*. 2017;35(19):2157-2164.
48. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.
49. Wedge E, Sengelov H, Hansen JW, et al. Improved Outcomes after Allogenic Hematopoietic Stem Cell Transplantation with Fludarabine/Treosulfan for Patients with Myelodysplastic Syndromes. *Biol Blood Marrow Transplant*. 2020;26(6):1091-1098.
50. Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *Lancet Haematol*. 2020;7(1):e28-e39.
51. Ruutu T, Volin L, Beelen DW, et al. Reduced-toxicity conditioning with treosulfan and fludarabine in allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes: final results of an international prospective phase II trial. *Haematologica*. 2011;96(9):1344-1350.

52. Sakellari I, Mallouri D, Gavriilaki E, et al. Survival Advantage and Comparable Toxicity in Reduced-Toxicity Treosulfan-Based versus Reduced-Intensity Busulfan-Based Conditioning Regimen in Myelodysplastic Syndrome and Acute Myeloid Leukemia Patients after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2017;23(3):445-451.
53. Modi D, Kim S, Singh V, et al. Pre-transplant hypomethylating agents do not influence post-transplant survival in myelodysplastic syndrome. *Leuk Lymphoma*. 2019;60(11):2762-2770.
54. Schroeder T, Wegener N, Lauseker M, et al. Comparison between Upfront Transplantation and different Pretransplant Cytoreductive Treatment Approaches in Patients with High-Risk Myelodysplastic Syndrome and Secondary Acute Myelogenous Leukemia. *Biol Blood Marrow Transplant*. 2019;25(8):1550-1559.
55. de Witte TM, Bowen D, Robin M, et al. Should patients with high-risk or transformed myelodysplastic syndrome proceed directly to allogeneic transplant without prior cytoreduction by remission-induction chemotherapy or hypomethylating agent therapy? *Clin Lymphoma Myeloma Leuk*. 2014;14 Suppl:S42-45.
56. Sorror ML. How I assess comorbidities before hematopoietic cell transplantation. *Blood*. 2013;121(15):2854-2863.
57. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10(3):223-232.
58. Fenaux P, Gattermann N, Seymour JF, et al. Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: azacitidine compared with low dose ara-C. *Br J Haematol*. 2010;149(2):244-249.
59. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia*. 2011;25(7):1147-1152.
60. Ravandi F, Issa JP, Garcia-Manero G, et al. Superior outcome with hypomethylating therapy in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome and chromosome 5 and 7 abnormalities. *Cancer*. 2009;115(24):5746-5751.
61. Seymour JF, Fenaux P, Silverman LR, et al. Effects of azacitidine compared with conventional care regimens in elderly (>/= 75 years) patients with higher-risk myelodysplastic syndromes. *Crit Rev Oncol Hematol*. 2010;76(3):218-227.
62. Skead G, Govender D. Gene of the month: MET. *J Clin Pathol*. 2015;68(6):405-409.
63. Tobiasson M, McLornan DP, Karimi M, et al. Mutations in histone modulators are associated with prolonged survival during azacitidine therapy. *Oncotarget*. 2016;7(16):22103-22115.
64. Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. *Cancer*. 2011;117(12):2697-2702.
65. Santini V, Fenaux P, Mufti GJ, et al. Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*. *Eur J Haematol*. 2010;85(2):130-138.
66. Field T, Perkins J, Huang Y, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2010;45(2):255-260.
67. Kim DY, Lee JH, Park YH, et al. Feasibility of hypomethylating agents followed by allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome. *Bone Marrow Transplant*. 2012;47(3):374-379.
68. Bennett JM, Young MS, Liesveld JL, et al. Phase II study of combination human recombinant GM-CSF with intermediate-dose cytarabine and mitoxantrone chemotherapy in

patients with high-risk myelodysplastic syndromes (RAEB, RAEBT, and CMML): an Eastern Cooperative Oncology Group Study. *Am J Hematol*. 2001;66(1):23-27.
69. Bernasconi P, Cavigliano PM, Genini E, et al. A complex translocation (5;7) in a patient with acute nonlymphocytic leukemia evolved from a myelodysplastic syndrome. *Cancer Genet Cytogenet*. 1998;105(2):182-186.
70. de Witte T, Suciu S, Peetermans M, et al. Intensive chemotherapy for poor prognosis myelodysplasia (MDS) and secondary acute myeloid leukemia (sAML) following MDS of more than 6 months duration. A pilot study by the Leukemia Cooperative Group of the European Organisation for Research and Treatment in Cancer (EORTC-LCG). *Leukemia*. 1995;9(11):1805-1811.
71. Hast R, Hellstrom-Lindberg E, Ohm L, et al. No benefit from adding GM-CSF to induction chemotherapy in transforming myelodysplastic syndromes: better outcome in patients with less proliferative disease. *Leukemia*. 2003;17(9):1827-1833.
72. Knipp S, Hildebrand B, Kundgen A, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. *Cancer*. 2007;110(2):345-352.
73. Fenaux P, Morel P, Rose C, Lai JL, Jouet JP, Bauters F. Prognostic factors in adult de novo myelodysplastic syndromes treated by intensive chemotherapy. *Br J Haematol*. 1991;77(4):497-501.
74. Invernizzi R, Pecci A, Rossi G, et al. Idarubicin and cytosine arabinoside in the induction and maintenance therapy of high-risk myelodysplastic syndromes. *Haematologica*. 1997;82(5 Suppl):9-12.
75. de Witte T, Hermans J, Vossen J, et al. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol*. 2000;110(3):620-630.
76. de Witte T, Suciu S, Verhoef G, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. *Blood*. 2001;98(8):2326-2331.
77. Denzlinger C, Bowen D, Benz D, Gelly K, Brugger W, Kanz L. Low-dose melphalan induces favourable responses in elderly patients with high-risk myelodysplastic syndromes or secondary acute myeloid leukaemia. *Br J Haematol*. 2000;108(1):93-95.
78. Omoto E, Deguchi S, Takaba S, et al. Low-dose melphalan for treatment of high-risk myelodysplastic syndromes. *Leukemia*. 1996;10(4):609-614.
79. Robak T, Szmigielska-Kaplon A, Urbanska-Rys H, Chojnowski K, Wrzesien-Kus A. Efficacy and toxicity of low-dose melphalan in myelodysplastic syndromes and acute myeloid leukemia with multilineage dysplasia. *Neoplasma*. 2003;50(3):172-175.
80. Cheson BD, Simon R. Low-dose ara-C in acute nonlymphocytic leukemia and myelodysplastic syndromes: a review of 20 years' experience. *Semin Oncol*. 1987;14(2 Suppl 1):126-133.
81. Hellstrom-Lindberg E, Robert KH, Gahrton G, et al. A predictive model for the clinical response to low dose ara-C: a study of 102 patients with myelodysplastic syndromes or acute leukaemia. *Br J Haematol*. 1992;81(4):503-511.
82. Miller KB, Kim K, Morrison FS, et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study. *Ann Hematol*. 1992;65(4):162-168.
83. Mughal TI, Cross NC, Padron E, et al. An International MDS/MPN Working Group's perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms. *Haematologica*. 2015;100(9):1117-1130.

84. Itzykson R, Fenaux P, Bowen D, et al. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults: Recommendations From the European Hematology Association and the European LeukemiaNet. *Hemasphere*. 2018;2(6):e150.
85. Elena C, Galli A, Such E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. *Blood*. 2016;128(10):1408-1417.
86. Such E, Germing U, Malcovati L, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. *Blood*. 2013;121(15):3005-3015.
87. Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. *Leukemia*. 2014;28(11):2206-2212.
88. Patnaik MM, Zahid MF, Lasho TL, et al. Number and type of TET2 mutations in chronic myelomonocytic leukemia and their clinical relevance. *Blood Cancer J*. 2016;6(9):e472.
89. Onida F, Kantarjian HM, Smith TL, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. *Blood*. 2002;99(3):840-849.
90. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol*. 2007;25(23):3503-3510.
91. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2018 update on diagnosis, risk stratification and management. *Am J Hematol*. 2018;93(6):824-840.
92. Liu HD, Ahn KW, Hu ZH, et al. Allogeneic Hematopoietic Cell Transplantation for Adult Chronic Myelomonocytic Leukemia. *Biol Blood Marrow Transplant*. 2017;23(5):767-775.
93. Itonaga H, Iwanaga M, Aoki K, et al. Impacts of graft-versus-host disease on outcomes after allogeneic hematopoietic stem cell transplantation for chronic myelomonocytic leukemia: A nationwide retrospective study. *Leuk Res*. 2016;41:48-55.
94. Symeonidis A, van Biezen A, de Wreede L, et al. Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. *Br J Haematol*. 2015;171(2):239-246.
95. Woo J, Choi DR, Storer BE, et al. Impact of clinical, cytogenetic, and molecular profiles on long-term survival after transplantation in patients with chronic myelomonocytic leukemia. *Haematologica*. 2020;105(3):652-660.
96. Ball BJ, Famulare CA, Stein EM, et al. Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure. *Blood Adv*. 2020;4(13):2866-2870.
97. Jadersten M, Boriskina K, Lindholm C, et al. Limited benefit in patients with MDS receiving venetoclax and azacitidine as a bridge to allogeneic stem cell transplantation. *Leuk Lymphoma*. 2021:1-4.
98. Welch JS, Petti AA, Miller CA, et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. *N Engl J Med*. 2016;375(21):2023-2036.
99. Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol*. 2012;30(27):3376-3382.
100. Thol F, Friesen I, Damm F, et al. Prognostic significance of ASXL1 mutations in patients with myelodysplastic syndromes. *J Clin Oncol*. 2011;29(18):2499-2506.
101. Gelsi-Boyer V, Trouplin V, Adelaide J, et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br J Haematol*. 2009;145(6):788-800.

102. Boultwood J, Perry J, Pellagatti A, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia*. 2010;24(5):1062-1065.
103. Della Porta MG, Galli A, Bacigalupo A, et al. Clinical Effects of Driver Somatic Mutations on the Outcomes of Patients With Myelodysplastic Syndromes Treated With Allogeneic Hematopoietic Stem-Cell Transplantation. *J Clin Oncol*. 2016.
104. Patnaik MM, Lasho TL, Finke CM, et al. Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing. *Am J Hematol*. 2016;91(5):492-498.
105. Damm F, Chesnais V, Nagata Y, et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. *Blood*. 2013;122(18):3169-3177.
106. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia. *N Engl J Med*. 2015;373(1):35-47.
107. Babushok DV, Perdigones N, Perin JC, et al. Emergence of clonal hematopoiesis in the majority of patients with acquired aplastic anemia. *Cancer Genet*. 2015;208(4):115-128.
108. Cui Y, Li B, Gale RP, et al. CSF3R, SETBP1 and CALR mutations in chronic neutrophilic leukemia. *J Hematol Oncol*. 2014;7:77.
109. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med*. 2013;368(19):1781-1790.
110. Pardanani A, Lasho TL, Laborde RR, et al. CSF3R T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. *Leukemia*. 2013;27(9):1870-1873.
111. Tefferi A, Thiele J, Vannucchi AM, Barbui T. An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. *Leukemia*. 2014;28(7):1407-1413.
112. Bacher U, Haferlach C, Schnittger S, Kohlmann A, Kern W, Haferlach T. Mutations of the TET2 and CBL genes: novel molecular markers in myeloid malignancies. *Ann Hematol*. 2010;89(7):643-652.
113. Barresi V, Palumbo GA, Musso N, et al. Clonal selection of 11q CN-LOH and CBL gene mutation in a serially studied patient during MDS progression to AML. *Leuk Res*. 2010;34(11):1539-1542.
114. Kao HW, Sanada M, Liang DC, et al. A high occurrence of acquisition and/or expansion of C-CBL mutant clones in the progression of high-risk myelodysplastic syndrome to acute myeloid leukemia. *Neoplasia*. 2011;13(11):1035-1042.
115. Schwaab J, Ernst T, Erben P, et al. Activating CBL mutations are associated with a distinct MDS/MPN phenotype. *Ann Hematol*. 2012;91(11):1713-1720.
116. Shiba N, Hasegawa D, Park MJ, et al. CBL mutation in chronic myelomonocytic leukemia secondary to familial platelet disorder with propensity to develop acute myeloid leukemia (FPD/AML). *Blood*. 2012;119(11):2612-2614.
117. Polprasert C, Schulze I, Sekeres MA, et al. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. *Cancer Cell*. 2015;27(5):658-670.
118. Walter MJ, Ding L, Shen D, et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. *Leukemia*. 2011;25(7):1153-1158.
119. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al. Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. *Blood*. 2015;125(3):499-503.
120. Lasho TL, Finke CM, Zblewski D, et al. Novel recurrent mutations in ethanolamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosinophilia and chronic myelomonocytic leukemia. *Blood Cancer J*. 2015;5:e275.
121. Patnaik MM, Barraco D, Lasho TL, et al. Targeted next generation sequencing and identification of risk factors in World Health Organization defined atypical chronic myeloid leukemia. *Am J Hematol*. 2017;92(6):542-548.

122. Wang Q, Dong S, Yao H, et al. ETV6 mutation in a cohort of 970 patients with hematologic malignancies. *Haematologica*. 2014;99(10):e176-178.
123. Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet*. 2015;47(2):180-185.
124. Ernst T, Chase AJ, Score J, et al. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. *Nat Genet*. 2010;42(8):722-726.
125. Nikoloski G, Langemeijer SM, Kuiper RP, et al. Somatic mutations of the histone methyltransferase gene EZH2 in myelodysplastic syndromes. *Nat Genet*. 2010;42(8):665-667.
126. Collin M, Dickinson R, Bigley V. Haematopoietic and immune defects associated with GATA2 mutation. *Br J Haematol*. 2015;169(2):173-187.
127. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nat Genet*. 2011;43(10):1012-1017.
128. Hsu AP, Sampaio EP, Khan J, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood*. 2011;118(10):2653-2655.
129. Pasquet M, Bellanne-Chantelot C, Tavitian S, et al. High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. *Blood*. 2013;121(5):822-829.
130. Wlodarski MW, Hirabayashi S, Pastor V, et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood*. 2016;127(11):1387-1397; quiz 1518.
131. Patnaik MM, Hanson CA, Hodnefield JM, et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. *Leukemia*. 2012;26(1):101-105.
132. Jin J, Hu C, Yu M, et al. Prognostic value of isocitrate dehydrogenase mutations in myelodysplastic syndromes: a retrospective cohort study and meta-analysis. *PLoS One*. 2014;9(6):e100206.
133. Thol F, Weissinger EM, Krauter J, et al. IDH1 mutations in patients with myelodysplastic syndromes are associated with an unfavorable prognosis. *Haematologica*. 2010;95(10):1668-1674.
134. DiNardo CD, Jabbour E, Ravandi F, et al. IDH1 and IDH2 mutations in myelodysplastic syndromes and role in disease progression. *Leukemia*. 2016;30(4):980-984.
135. Lin CC, Hou HA, Chou WC, et al. IDH mutations are closely associated with mutations of DNMT3A, ASXL1 and SRSF2 in patients with myelodysplastic syndromes and are stable during disease evolution. *Am J Hematol*. 2014;89(2):137-144.
136. Stieglitz E, Taylor-Weiner AN, Chang TY, et al. The genomic landscape of juvenile myelomonocytic leukemia. *Nat Genet*. 2015;47(11):1326-1333.
137. Mori T, Nagata Y, Makishima H, et al. Somatic PHF6 mutations in 1760 cases with various myeloid neoplasms. *Leukemia*. 2016;30(11):2270-2273.
138. Hsu JI, Dayaram T, Tovy A, et al. PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. *Cell Stem Cell*. 2018;23(5):700-713 e706.
139. Kahn JD, Miller PG, Silver AJ, et al. PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. *Blood*. 2018;132(11):1095-1105.
140. Hugues L, Cave H, Philippe N, Pereira S, Fenaux P, Preudhomme C. Mutations of PTPN11 are rare in adult myeloid malignancies. *Haematologica*. 2005;90(6):853-854.
141. Loh ML, Martinelli S, Cordeddu V, et al. Acquired PTPN11 mutations occur rarely in adult patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Leuk Res*. 2005;29(4):459-462.

142. Tartaglia M, Niemeyer CM, Fragale A, et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. *Nat Genet*. 2003;34(2):148-150.
143. Kon A, Shih LY, Minamino M, et al. Recurrent mutations in multiple components of the cohesin complex in myeloid neoplasms. *Nat Genet*. 2013;45(10):1232-1237.
144. Thol F, Bollin R, Gehlhaar M, et al. Mutations in the cohesin complex in acute myeloid leukemia: clinical and prognostic implications. *Blood*. 2014;123(6):914-920.
145. Thota S, Viny AD, Makishima H, et al. Genetic alterations of the cohesin complex genes in myeloid malignancies. *Blood*. 2014;124(11):1790-1798.
146. Fernandez-Mercado M, Pellagatti A, Di Genua C, et al. Mutations in SETBP1 are recurrent in myelodysplastic syndromes and often coexist with cytogenetic markers associated with disease progression. *Br J Haematol*. 2013;163(2):235-239.
147. Inoue D, Kitaura J, Matsui H, et al. SETBP1 mutations drive leukemic transformation in ASXL1-mutated MDS. *Leukemia*. 2015;29(4):847-857.
148. Makishima H, Yoshida K, Nguyen N, et al. Somatic SETBP1 mutations in myeloid malignancies. *Nat Genet*. 2013;45(8):942-946.
149. 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.
150. Piazza R, Valletta S, Winkelmann N, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. *Nat Genet*. 2013;45(1):18-24.
151. Papaemmanuil E, Cazzola M, Boultwood J, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med*. 2011;365(15):1384-1395.
152. Patnaik MM, Lasho TL, Hodnefield JM, et al. SF3B1 mutations are prevalent in myelodysplastic syndromes with ring sideroblasts but do not hold independent prognostic value. *Blood*. 2012;119(2):569-572.
153. Damm F, Kosmider O, Gelsi-Boyer V, et al. Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. *Blood*. 2012;119(14):3211-3218.
154. Malcovati L, Papaemmanuil E, Bowen DT, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood*. 2011;118(24):6239-6246.
155. Mian SA, Smith AE, Kulasekararaj AG, et al. Spliceosome mutations exhibit specific associations with epigenetic modifiers and proto-oncogenes mutated in myelodysplastic syndrome. *Haematologica*. 2013;98(7):1058-1066.
156. Thol F, Kade S, Schlarmann C, et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. *Blood*. 2012;119(15):3578-3584.
157. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature*. 2011;478(7367):64-69.
158. Wu SJ, Kuo YY, Hou HA, et al. The clinical implication of SRSF2 mutation in patients with myelodysplastic syndrome and its stability during disease evolution. *Blood*. 2012;120(15):3106-3111.
159. Cui Y, Tong H, Du X, et al. Impact of TET2, SRSF2, ASXL1 and SETBP1 mutations on survival of patients with chronic myelomonocytic leukemia. *Exp Hematol Oncol*. 2015;4:14.
160. Hong JY, Seo JY, Kim SH, et al. Mutations in the Spliceosomal Machinery Genes SRSF2, U2AF1, and ZRSR2 and Response to Decitabine in Myelodysplastic Syndrome. *Anticancer Res*. 2015;35(5):3081-3089.

161. Kang MG, Kim HR, Seo BY, et al. The prognostic impact of mutations in spliceosomal genes for myelodysplastic syndrome patients without ring sideroblasts. *BMC Cancer*. 2015;15:484.
162. Kim E, Ilagan JO, Liang Y, et al. SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition. *Cancer Cell*. 2015;27(5):617-630.
163. Komeno Y, Huang YJ, Qiu J, et al. SRSF2 Is Essential for Hematopoiesis, and Its Myelodysplastic Syndrome-Related Mutations Dysregulate Alternative Pre-mRNA Splicing. *Mol Cell Biol*. 2015;35(17):3071-3082.
164. Makishima H, Visconte V, Sakaguchi H, et al. Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. *Blood*. 2012;119(14):3203-3210.
165. Zhang SJ, Rampal R, Manshouri T, et al. Genetic analysis of patients with leukemic transformation of myeloproliferative neoplasms shows recurrent SRSF2 mutations that are associated with adverse outcome. *Blood*. 2012;119(19):4480-4485.
166. Smith AE, Mohamedali AM, Kulasekararaj A, et al. Next-generation sequencing of the TET2 gene in 355 MDS and CMML patients reveals low-abundance mutant clones with early origins, but indicates no definite prognostic value. *Blood*. 2010;116(19):3923-3932.
167. Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. *Blood*. 2014;124(17):2705-2712.
168. Bejar R, Stevenson KE, Caughey B, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2014;32(25):2691-2698.
169. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. *Nat Genet*. 2012;44(11):1179-1181.
170. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. *N Engl J Med*. 2009;360(22):2289-2301.
171. Kosmider O, Gelsi-Boyer V, Cheok M, et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). *Blood*. 2009;114(15):3285-3291.
172. Langemeijer SM, Kuiper RP, Berends M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. *Nat Genet*. 2009;41(7):838-842.
173. Sallman DA, Komrokji R, Vaupel C, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. *Leukemia*. 2016;30(3):666-673.
174. Sebaa A, Ades L, Baran-Marzack F, et al. Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid leukemia with 5q deletion. *Genes Chromosomes Cancer*. 2012;51(12):1086-1092.
175. Graubert TA, Shen D, Ding L, et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. *Nat Genet*. 2011;44(1):53-57.
176. Przychodzen B, Jerez A, Guinta K, et al. Patterns of missplicing due to somatic U2AF1 mutations in myeloid neoplasms. *Blood*. 2013;122(6):999-1006.
177. Madan V, Kanojia D, Li J, et al. Aberrant splicing of U12-type introns is the hallmark of ZRSR2 mutant myelodysplastic syndrome. *Nat Commun*. 2015;6:6042.