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An Evaluation of Current Diagnostic Approaches for Patients with Myelodysplastic Syndromes

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Introduction

Myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by morphologic dysplasia in the bone marrow as well as cytopenia in peripheral blood. MDS are diseases of the elderly, usually arising in patients aged 70 years and older. However, it may develop in younger patients as well, especially in patients harboring a germline predisposition. Due to the heterogeneity of the disease, an accurate diagnosis may be challenging as the patients' clinical presentation as well as diagnostic findings may be subtle.

Based on the number of dysplastic cell lineages, the proportion of blasts in the bone marrow and peripheral blood, and the type of cytogenetic changes, MDS are divided into different subtypes according to the current WHO classification of 2022 [1]. WHO subtypes are associated with different overall survival rates as well as different risks of evolution into acute myeloid leukemia (AML). Therapeutic decisions are made by considering patient-related factors, like age, performance status, and comorbidities, and disease-related variables, such as genetic alterations, degree of cytopenia and percentage of blasts. Risk stratification in clinical practice is based on the Revised International Prognostic Scoring System (IPSS-R) [2], considering hemoglobin level, absolute neutrophil count, platelet counts, bone marrow blast percentage as well as cytogenetic findings. The IPSS-R defines five risk categories, stratifying the underlying MDS subtype into lower and higher risk disease which enables a risk-adapted therapeutic approach.

Disease pathogenesis

Understanding the pathogenesis of ineffective hematopoiesis is crucial for identifying therapeutic targets in MDS. MDS typically arise from a small subclone, harboring cytogenetic as well as molecular aberrations. At the time of initial diagnosis multiple mutations and cytogenetic aberrations may be present in one MDS patient. Some mutated genes might play an important role in MDS pathogenesis and blast proliferation (driver mutations with oncogenic potential), while other non-pathogenic ones appear during the course of the disease and then expand together with pathogenic mutations (passenger mutations). Over the course of the disease, a patient with MDS often acquires several mutations in various subclones. This genetic diversity results in a group of diseases, which is difficult diagnose, prognosticate, and treat.

Over the past decades, diagnostic approaches beyond morphologic examination of blood and bone marrow specimens gained importance in diagnosing MDS. Especially cytogenetic and mutational testing revealed the complexity of MDS and aided in understanding the cytogenetic and molecular landscape of various MDS subtypes, which in turn contributes to prognostic stratification and a more patient-tailored therapeutic approach. In the following we will give a brief overview over the common diagnostic tools and their value in clinical practice.

Up-to-date diagnostic approaches

Morphologic examination of blood and bone marrow specimens

As defined by the current WHO classification of 2022, morphologic examination of a bone marrow aspirate, bone marrow trephine biopsy and peripheral blood is still a cornerstone for the diagnosis of MDS [1]. Three WHO subtypes are only defined by morphologic features, i.e. hypoplastic MDS, MDS with fibrosis and MDS with increased blasts. Morphological evaluation therefore is focused on the assessment of myeloid dysplasia, including the enumeration of ring sideroblasts as well as blasts in bone marrow specimens and peripheral blood, and assessment of cellularity and fibrosis by means of trephine biopsy. To achieve the highest diagnostic quality, at least 500 cells in a bone marrow aspirate, a minimum of 100 erythroblasts as well as 40 megakaryocytes should be evaluated, whenever possible [3]. Morphologic assessment may, however, be challenging due to diverse morphologic findings, hypocellular marrows or fibrosis lowering the quality of bone marrow aspirate specimens. Furthermore, even though morphologic examination might seem simple and easily available, morphological changes are often subtle and require a great expertise by experienced hemopathologists and hematologists. The presence of multilineage dysplasia and/or an increased medullary blast count however indicates an underlying myeloid malignancy in the vast majority of cases. If only unilineage dysplasia without increased medullary blast

count and without ring sideroblasts is present, the diagnosis of MDS is supported by genetic examination to detect clonality.

Immunophenotyping in MDS

Multiparameter flow cytometry is widely used to detect aberrant antigen expression in hematologic neoplasms as well as to identify abnormal phenotypes in maturing hematopoiesis but does not directly impact the WHO classification.

Immunophenotyping in MDS relies on two principles: identifying qualitative changes in antigen expression especially in maturing hematopoietic cells on the one hand and detecting elevated blast counts by furthermore identifying myeloid progenitors, on the other hand [4]. Even though flow cytometry is widely available, its interpretation may be challenging for several reasons. As MDS is a rather heterogenetic group of diseases, some documented abnormalities are only detected on a subpopulation of cells. Furthermore, those changes involve aberrant antigen expression (lymphoid antigen expression on myeloid cells), asynchronous antigen expression (CD34 expression in mature myeloid cells) and altered intensity of expression. Another pitfall in immunophenotyping is that abnormalities may be expressed throughout all maturational stages. Hence, choosing the right antibody panel and gating strategy is essential and more difficult than in hematologic neoplasms where neoplastic populations are more homogeneous. Finally, abnormalities are not specific for MDS, as similar aberrations in antigen expression might be present in patients with reactive bone marrow conditions or even in other myeloid disorders [5].

Cytogenetics in MDS

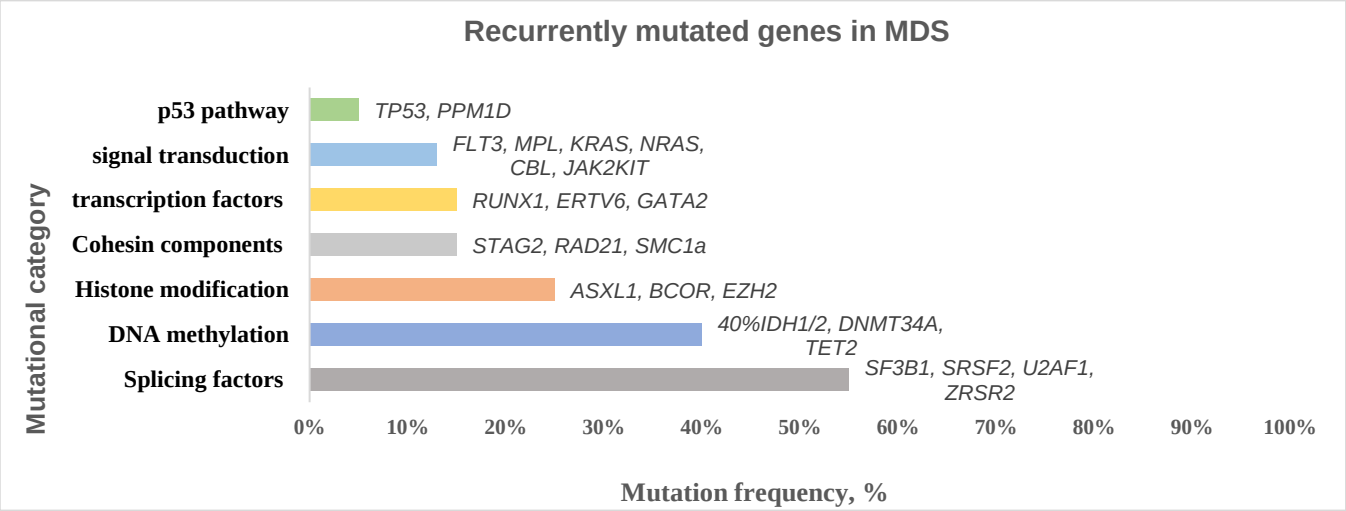
About 50-60% of newly diagnosed MDS cases present with cytogenetic abnormalities, which can be detected by applying conventional karyotype banding analysis and provide proof of clonality. Cytogenetic aberrations are important prognostic parameters, which is reflected in the IPSS as well as in its revised versions. Most importantly, some cytogenetic aberrations bear therapeutic approaches: In cases of MDS del(5q) for instance, the angiogenesis inhibitor Lenalidomide is a therapeutic option. The cytogenetic landscape in MDS is as heterogeneous as morphology. A large registry study identified more than 680 cytogenetic aberrations in newly diagnosed MDS [6]. The most common cytogenetic alterations in MDS are del(5q), monosomy 7/del(7q), trisomy 8, loss of Y, and complex karyotypes (conventionally defined as ≥3 chromosomal aberrations, including at least 1 structural aberration), especially in patients with MDS arising after prior cytotoxic therapy [7]. About 80% of patients with secondary MDS harbor cytogenetic aberrations. As an important addendum, fluorescence in-situ hybridization (FISH) analyses can be applied to both, metaphases, and interphase cell nuclei. It improves diagnostic value, especially in-patient samples with poor-quality metaphases or submicroscopic aberrations. However, FISH analysis ability in accurate detection of cytogenetic aberrations is limited. It should therefore primarily be used when blood or bone marrow specimens are inadequate for conventional cytogenetic G-banding. Another important diagnostic value of cytogenetic testing is that is demonstrates a concordance between peripheral blood and bone marrow samples. If a patient has a sufficient white blood cell count in the peripheral blood, follow-up cytogenetic analyses may even be performed using peripheral blood, making repeated bone marrow biopsies unnecessary. When FISH is performed on CD34+ selected peripheral mononuclear cells, this technique can serve as a genetic follow up tool [8].

Genomics in MDS

Genetic analyses have become increasingly important in recent decades. Especially the introduction of DNA sequencing, known as next generation sequencing (NGS), allows a better characterization of the molecular landscape and identification of potential therapeutic targets. MDS typically emerges from the development and growth of a somatically mutated clone of hematopoietic progenitor cells. Several mutated driver genes may cause proliferation; biologic pathways include RNA splicing genes, DNA methylation, histone modification, transcription regulation, DNA repair control, DNA signaling, and mutations in the cohesin complex. Studies analyzing next generation sequencing of various myeloid genes in MDS patients showed that approximately 90% of MDS patients harbor at least one oncogenic mutation at time of initial diagnosis [9]. Mutation-driver genes provide an advantage to the hematopoietic stem cell and progenitor level, determining clonal proliferation, but this is associated with a disadvantage at the hematopoietic precursor level, leading to ineffective hematopoiesis and peripheral blood cytopenia. Oncogenic mutations may therefore initiate the disease or change during the course of the disease. However, there are no molecular alterations which are specific for MDS. Many recurrent somatic mutations are shared with other myeloid neoplasms, especially CMML and AML.

Mutations in driver genes occur in diverse pathways and can impact disease phenotype, overall survival as well as progression to secondary AML Mutations can be organized into subgroups which correspond with a specific mode of action on a cellular basis: RNA-splicing factors, epigenetic regulators, cohesin components, transcriptional factors, DNA damage and signal transduction molecules (Figure 1). The presence of any somatic mutation in patients with MDS can support the diagnosis by proving clonality.

Figure 1: Frequency of recurrently mutated somatic genes in MDS according to cellular mode of action.



Molecular aberrations with classificatory, prognostic and therapeutic consequences

The current WHO 2022 classification relies on molecular aberrations in addition to morphology and conventional banding analyses. The provisional category "MDS with biallelic TP53 alteration" has been proposed due to the very poor prognosis of these patients and does no longer take into account morphologic or hematologic features of blood and marrow [10]. However, chromosomal analyses are mandatory as in the majority of these patients the biallelic TP53 alteration is a result from one mutation in combination with -17p or -17, mostly within a complex karyotype. The WHO subgroup "MDS with SF3B1 mutation" is genetically defined, but there is a strong genotype-phenotype correlation, as more than 90% of the patients with SF3B1 mutation present with ring sideroblasts in the marrow. Patients with SF3B1 mutation and thrombocytosis of more than 450.000/µl belong to the group of MDS-MPN neoplasms. Finally, MDS patients presenting with deletions on chromosome 5q may also harbor monoallelic TP53 mutations, indicating a worse prognosis with regard to leukemia-free survival and a shorter duration of response to Lenaliomide. Hence, from a diagnostic point of view, NGS analyses including SF3B1 and TP53 are mandatory in order to correctly apply the current WHO classification.

From the prognostic point of view, somatic mutations have been shown to have important impact on patient´s overall survival as well as leukemia-free survival. Mutations in genes like TP53, RUNX1, ASXL1, and SRSF2 deteriorate overall survival independently, whereas the presence of SF3B1 mutation is associated with a better survival as compared to patients with wild type SF3B1. However, the prognostic impact of other genetic alterations, such as TET2 and DNMT3A, is under debate [12]. Aside from the mutational status in a binary method (ie, the mutation is present or absent), other mutational characteristics like the variant allele frequency (VAF), the type of mutations (missense vs other mutational types), and co-mutated genes play a crucial role. Somatic mutations occur in MDS patients as well as in otherwise healthy, older aged individuals. The type and frequency of mutations might differ. Somatic mutations in the spliceosome apparatus (SF3B1, SRSF2, U2AF1) and TP53 are more common in MDS, while mutations in FLT3, NPM1 and IDH1/2 often define de novo AML [11].

The clonal burden of each mutation, especially defined by the VAF, bears implications on the level of clonal expansion and/or evolution and the chronology in which the genes suffered mutational changes. Early events in clonal evolution typically present with high VAF, as they accumulate clonal burden during the course of the disease. Early events are mutations in spliceosome genes, ASXL1 or TET2 mutations [11]. Mutational changes in ASXL1 are present in approximately 20-25% of MDS patients and have a negative impact on the prognosis of myeloid malignancies in general. Somatic mutations in the TET2 gene inhibit DNA demethylation, leading to hypermethylation, which contributes to stem cell proliferation [12]. Mutations in TET2 are frequent and seen in up to 35% of patients with MDS. Events resulting in a lower VAF, subclonal events, drive clonal evolution to higher risk MDS or accelerate the disease to progression into AML. Commonly involved are transcription factors such as RUNX1, and genes involved in signal transduction like FLT3 and RAS [9].

Amongst the commonly recurrent mutated genes, patients with TP53 mutant MDS show the worst outcome and account for approximately 10% of de novo MDS and up to 40% of MDS with prior cytotoxic therapy. Median overall survival is about 12 months only. It is associated with a complex karyotype, and clonal burden as well as higher VAF correlate with inferior overall survival [13]. One-third of MDS patients with TP53 mutations present with monoallelic TP53 mutation, while two-thirds have multiple hits or even losses of the TP53 gene. Biallelic TP53 mutations are strongly associated with complex karyotypes and a poorer prognosis compared to monoallelic mutations. Table 1 gives a broad overview of recurrent mutated somatic genes in MDS, their frequency and their prognostic relevance.

Table 1: Frequently mutated somatic genes in patients with MDS and their prognostic relevance**.**

MUTATED GENES	FREQUENCY	CLINICAL ASSOCIATIONS	PROGNOSTIC AND THERAPEUTIC RELEVANCE
ASXL1	10-20%	- Pts present with elevated bone marrow blasts, intermediate-risk karyotype, and co-mutations of various other genes	- Negative prognostic marker for MDS and CMML pts, especially after alloSCT [14]
TET2	20-30%	- frequently associated with normal karyotype - commonly seen in CMML	- increased response to hypomethylating agents, especially when present at high VAFs [15] - predicts shorter OS in treated pts
DNMT3A	15%	- early event in disease evolution - associated with MDS-MLD or MDS-EB	- linked to a higher risk of transformation into AML, shorter OS [16]
IDH1* AND *IDH2	<5%	- frequently mutated in AML	- prognostic impact is still under review - IDH inhibitors enasidenib and ivosidenib in r/r AML [17]
RUNX1	10%	- Frequently associated with AML following MDS - Thrombocytopenia is common at initial diagnosis	- Negative prognostic marker - Shorter OS following alloSCT [18]
NRAS, KRAS	10%	- Late event in disease evolution - Higher frequencies in CMML and AML	- adverse prognostic marker, esp. in lower risk disease [19] - highly likely to transform into AML
TP53	5-10%	- Frequently associated with MDS secondary to cytotoxic therapy - closely linked to complex karyotypes	- common in pts after radio-chemotherapy - linked to dismal outcomes regardless of the applied therapy (HMA, alloSCT) [20] - adverse prognosis may depend on the mutation burden and allelic state [10]
PPM1D	<5%	- Frequent in pts with therapy related MDS	- no significant impact on outcomes known
NPM1	2%	- Common in de novo AML, less frequent in MDS	- associated with an aggressive MDS phenotype and a high progression risk to AML - intensive chemotherapy and alloSCT seem to improve outcomes [21]
SF3B1	15-30%	- Associated with ring sideroblastic phenotype, distinct WHO entity	- Disease with indolent course and favorable outcomes [22]

The above-mentioned IPSS-R is universally used in clinical decision making to find risk-adapted therapeutic approaches and is a very robust prognostic tool. However, the IPSS-R is limited due to not including molecular mutations. Since molecular lesions proved to be of independent prognostic significance as mentioned above, the International Working Group for Prognosis in MDS (IWG-PM) recently developed the International Prognostic Scoring System Molecular (IPSS-M). In contrast to previous scoring systems, the IPSS-M risk score was built as a continuous index, defined as a weighted total sum of the following prognostic variables: Hemoglobin level, platelet count, bone marrow blast percentage, IPSS-R cytogenetic categories, furthermore 17 binary features derived from the presence of mutations in 16 prognostic genes, and a feature representing the number of mutated genes from a residual group of 15 genes [23].

Clinical implications and challenges of molecular testing

The goal of genomic sequencing is to translate genetic findings into everyday clinical practice, by identifying the impact of mutations on prognosis, but also by identifying mutations as targets for specific drugs. Today, state of the art is to perform analyses not only on genetic aberrations for diagnostic purposes, but also for prognostication and clinical management, according to the latest European LeukemiaNet recommendation [24]. However, challenges occur when recurrent somatic mutations are found without significant dysplasia and combined with a normal karyotype, making diagnosis of MDS less obvious. While mutations in splicing factors like RUNX1 present with a high predictive value for a subsequent MDS diagnosis, other common mutations, such as TET2 or ASXL1, also occur in otherwise healthy individuals, usually with a very low VAF. Patients who either lack dysplasia in more than 10% of cells or do not display aberrant cytogenetics or elevated blast counts, and therefore subsequently do not fulfill WHO criteria for diagnosing MDS, are unclear. Bone marrow samples of patients with clonal hematopoiesis of indeterminate potential (CHIP) analyzed by next-generation sequencing revealed somatic mutations in up to 30% of patients [25]. The most frequent mutations are TET2, DNMT3A, ASXL1 and SRSF2, with VAF

varying from less than 10 up to 40%. CHIP has been shown to predispose for a higher risk of developing hematological neoplasms, especially MDS [26], but for cardiovascular events as well [27]. In patients with unexplained cytopenia or mild dysplasia, the identification of molecular aberrations in oncogenes might lead to earlier diagnosis and subsequently treatment initiation to meliorate prognosis [28]. So far, the sole rationale is to closely monitor patients displaying somatic mutations only, as not every myeloid precondition will progress into MDS [26].

Another implication of mutational data is to correlate distinct genotypes with phenotypes. Patients with TET2 as well as SRSF2 mutations display higher hemoglobin levels as well as higher monocyte counts compared with patients without these co-mutations. This highlights the importance of incorporating molecular data into classifications.

Apart from recurrent somatic mutations, MDS, especially in younger adults or even children, might arise from germline mutations. Germline mutations may lead to MDS, but they also increase the susceptibility to other myeloid neoplasms as described in Fanconi anemia and Dyskeratosis congenita, which may present with an MDS-like phenotype. A rapid recognition is of utmost importance, not only for the purpose of timely therapy but also for genetic counseling for other family members who might harbor germline mutations as well. A diagnostic approach should include an extended family history with focus on hematologic neoplasms and disorders as well as a personal history, including prior cytotoxic chemotherapy or radiotherapy, and an extensive physical exam, focusing on constitutional symptoms suggestive of hematopoietic insufficiency or bone marrow failure [29]. Cytogenetic and molecular genetic testing is mandatory, with special focus on genes which might be associated with germline mutations in MDS and other myeloid neoplasms. Panels for somatic MDS mutations should not be used since somatic gene panels might omit the regions or type of mutation of genes of interest. As previously mentioned, hematopoietic tissue can be affected by somatic mutations without clinical consequences. Many genes can be mutated somatically as well as constitutionally. The preferred tissue for screening for MDS predisposition syndromes is skin fibroblasts. While testing of peripheral blood might seem more convenient and expedient, it might lead to false-negative results by identifying somatic mutations. Hence, gold standard is analyzing non-hematopoietic tissue to distinguish somatic from germline mutations [30]. Testing of family members is recommended as well.

Assessment of minimal residual disease (MRD) by means molecular features is crucial in the context of allogeneic stem cell transplantation (alloSCT). Known MRD markers are chimerism analysis following alloSCT, flow cytometrical analyses, and analysis of WT1 expression levels [31]. Data in a pre-transplant setting, however, remains limited since discrimination between benign somatic mutations and malignant populations is challenging. Since the majority of MDS patients harbor a molecular aberration, a close monitoring of VAF levels of known mutations may provide prognostic information.

Recommendations on molecular analyses for daily practice

In order to properly diagnose and prognosticate patients with MDS a comprehensive examination of blood and marrow by cytomorphology, histology, chromosomal banding and FISH is mandatory and must be complemented by molecular analyses. The choice of the preferred tool to analyze the presence or absence of mutations strongly depends on the available technology in each institution. Along with the mode of operation, the number of genes analyzed within a somatic panel is infinite and should be chosen according to institutional capabilities and clinical question, too. A comprehensive panel applied for initial MDS diagnoses should include commonly mutated somatic genes but also rare genes with known hotspot mutations and germline mutations. A suggested panel is shown in Figure 2. In accordance with the new IPSS-M, we strongly suggest including at least the 16 prognostic genes, implementing genes which might be used for MRD detection following therapy as well.

Figure 2: Suggested comprehensive targeted myeloid disorder gene panel according to recommendations of the IPSS-M risk model including somatic as well as germline mutated genes.

TP53	KMT2A	FLT3	ASXL1	CBL
KRAS	IDH2	EZH2	ETV6	DNMT3A
NPM1	NRAS	RUNX1	SF3B1	SRSF2
U2AF1	BCOR	CEBPA	ETNK1	GATA2
PPM1D	PHF6	NF1	IDH1	GNB1
PRPF8	PTN11	SETBP1	STAG2	WT1

Mandatory genes, including 16 prognostic genes according to the IPSS-M

Residual genes to be included in extensive gene panels

Conclusion

Molecular genetic testing in MDS is needed to improve diagnostic approaches, to allow individualized treatment options in the future and to offer more precise possibilities for detecting MRD. Despite the rapid changes in our knowledge about the molecular landscape in MDS, molecular analyses are now an integral part of the diagnostic algorithm. We therefore recommend implementing a comprehensive but nonetheless targeted myeloid panel for every patient presenting with MDS. The goal in molecular genetic testing should be to provide further insight into the disease biology and to ameliorate already existing treatment options but foremost to develop targeted ones to offer the best treatment possible.

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