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Chapter

Cytogenetic and Genetic Advances in Myelodysplasia Syndromes

Mounia Bendari and Nisrine Khoubila

Abstract

Myelodysplasia syndromes (MDS) are defined by a heterogeneous group of myeloid malignancies characterized by peripheral blood cytopenia and dishematopoiesis and frequently progress to acute myeloid leukemia. Conventional karyotype has a crucial role in myelodysplastic syndrome (MDS) and is one of items of the International Prognostic Scoring System (IPSS) for patient risk stratification and treatment selection. Approximately 50–60% of cases of MDS present chromosomal abnormalities, like the deletions of chromosome 5q and 7q, trisomy 8, and complex karyotypes. New genomic technologies have been developted, like single-nucleotide polymorphism array and next-generation sequencing. They can identify the heterozygous deletions wich result in haplo-insufficient gene expression (e.g., CSNK1A1, DDX41 on chromosome 5, CUX1, LUC7L2, EZH2 on chromosome 7) involved in the pathogenesis of myelodysplasia syndromes. Genetic abnormalities are multiple, the most recurrent one are involved in the RNA splicing like SF3B1, SRSF2, U2AF1, ZRSR2, LUC7L2, and DDX41. Epigenetic modifications are also identified, such as histone modification as ASXL1, EZH2. Finally, it can be DNA methylation (e.g., TET2, DNMT3A, IDH1/IDH2). On this review we will summarize the most recent progress in molecular pathogenesis of MDS, and try to better understand the pathogenesis of the specific subgroups of MDS patients and applications of discovery of new genetic mutation in the development of new therapeutic.

Keywords: cytogenetic, new genomic technologies, IPSS-R, karyotype, myelodysplasia, single-nucleotide polymorphism array, next-generation sequencing

1. Introduction

Myelodysplastic syndromes (MDSs) comprises a heterogeneous group of myeloid neoplasms, they are characterized by pancytopenia, bone marrow (BM) hyperplasia, dysplasia, and cytopenias of the peripheral blood. The blast count may be normal or elevated but is less than 20% in the bone marrow and peripheral blood. MDS are characterized by elevated risk of progression to secondary acute myeloid leukemia (AML) [1, 2].

MDS is caused by accumulation of genetic or epigenetic (such as promoter hypermethyltion) lesions, first it s occurred in an immature progenitor and provides proliferative advantage of the MDS clone over normal immature progenitors.

MDS progenitors leads abnormal terminal differentiation and capacity to resist to apoptosis. These two features explain the clinical consequences of blast

accumulation and peripheral cytopenias. Microenvironmental changes and immune deregulation participate to this differentiation defect [3].

The purpose of this review is to overview the recent advances in the cytogenetics and genetics of MDS and related disorders.

2. Epidemiology

MDS's incidence increase markedly with age, and the classical patient will be in their late 60s or 70s and have one or more otherwise unexplained cytopenia [4, 5].

The incidence is 4 to 5 per 100,000 persons per year, the direct etiology for MDS is usually unknown. However, in 15 to 20% of cases, MDS are secondary (sMDS) to chemotherapy and/or radiotherapy for an other disease. Some times, MDS can be, secondary to exposure to benzene or other aromatic hydrocarbons, or products used in agriculture.

The pathophysiology of MDS and its progression to AML involve cytogenetic, genetic, and epigenetic factors [6].

Now, it is well recognized that MDS is, like other cancers, shaped by recursive rounds of positive selections, where gene mutations and other genetic alterations play central roles.

3. WHO Classification of MDS

The classification of Tumours of Haematopoetic and Lymphoid Tissues done by the World Health Organization (WHO) defines MDS as a clonal, stem cell disorder.

The 2016 new revision of this classification defines ten MDS subtypes. The first subtype is defined by MDS with single lineage dysplasia (MDS-SLD), the second one is characterized by MDS with dysplasia in two or more myeloid lineages (MDS-MLD). Third subtype is MDS-SLD/MLD with ≥15% ring sideroblasts (RSs; MDS-MLD-RS). An excess of blasts of up to 9% in bone marrow and up to 4% in peripheral blood define MDSEB- 1, and MDS with 10–19% bone marrow and 5–19% blood blasts define MDS-EB-2. An other subtype is present on this classification, it s MDS with isolated deletion of chromosome 5q [del(5q)]. Finally, we found MDS unclassifiable (MDS-U) based on defining cytogenetic abnormality, MDS-U with SLD and pancytopenia and MDS-U with 1% blood blasts [7].

Table 1 summarizes 2016 OMS classification of MDS.

4. Evolution/prognostic

Until 2016, del(5q) was the only genetic marker implicated in MDS classification. In the updated classification, identification of SF3B1 mutation determines MDS-RS (even when the RS count is >5–15%).

The revised International Prognostic Scoring System (IPSS-R) for MDS propose 5 risk groups depending on number and severity of cytopenia. Its include also the percentage of bone marrow blasts and cytogenetic aberrations **Figure 1** [7].

Cytogenetic abnormalities were categorized into 5 prognostic subgroups that were shown to have significant prognostic relevance with different median survival and risk of evolution into AML.

The molecular profile of MDS has become a vital factor in assessing the risk of patients with MDS and making treatment decisions. Health care providers must understand when to order genetic testing, how to interpret the results, and the

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1–3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multllineage dysplasia (MDS-RS-MLD)	2 or 3	1–3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills 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 –7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0–3	1–3	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
MDS-EB-2	0–3	1–3	None or any	BM 10–19% or PB 5–19% or Auer rods	Any

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1–3	1–3	None or any	BM <5%, PB – 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1–3	<15%	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1–3	1–3	None	BM <5%, PB <2%	Any

**Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10^9/L.*
†If SF3B1 mutation is present.
‡One percent PB blasts must be recorded on at least 2 separate occasions.

Table 1.
The World Health Organization (WHO) classification of Tumours of Haematopoetic and Lymphoid Tissues defines MDS.

Prognostic Variable	0	0.5	1.0	1.5	2.0	3	4
Cytogenetics*	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blasts (%)	≤2	—	>2% – <5%	—	5%–10%	>10%	—
Hemoglobin	≥10	—	8 – <10	<8	—	—	—
Platelets	≥100	50 – <100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

Scores for risk groups are as follows: Very low ≤1.5; Low >1.5–3; Intermediate >3–4.5; High >4.5–6; Very high >6.

ANC = absolute neutrophil count; BM = bone marrow.

*Cytogenetics: Very good: −Y, del(11q); Good: normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones; Poor: −7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities; Very poor: complex: >3 abnormalities.

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Figure 1.
International Prognostic Scoring System (IPSS).

Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival,* y	Median AML evolution, 25%,* y	Hazard ratios OS/AML*	Hazard ratios OS/AML†
Very good (4%*/3%†)	−Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13%*/19%†)	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4%*/5%†)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very poor (7%*/7%†)	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

OS indicates overall survival; and NR, not reached.
*Data from patients in this IWG-PM database, multivariate analysis (n = 7012).
†Data from Schanz et al[8] (n = 2754).

Figure 2.
Revised International Prognostic Scoring System (IPSS-R).

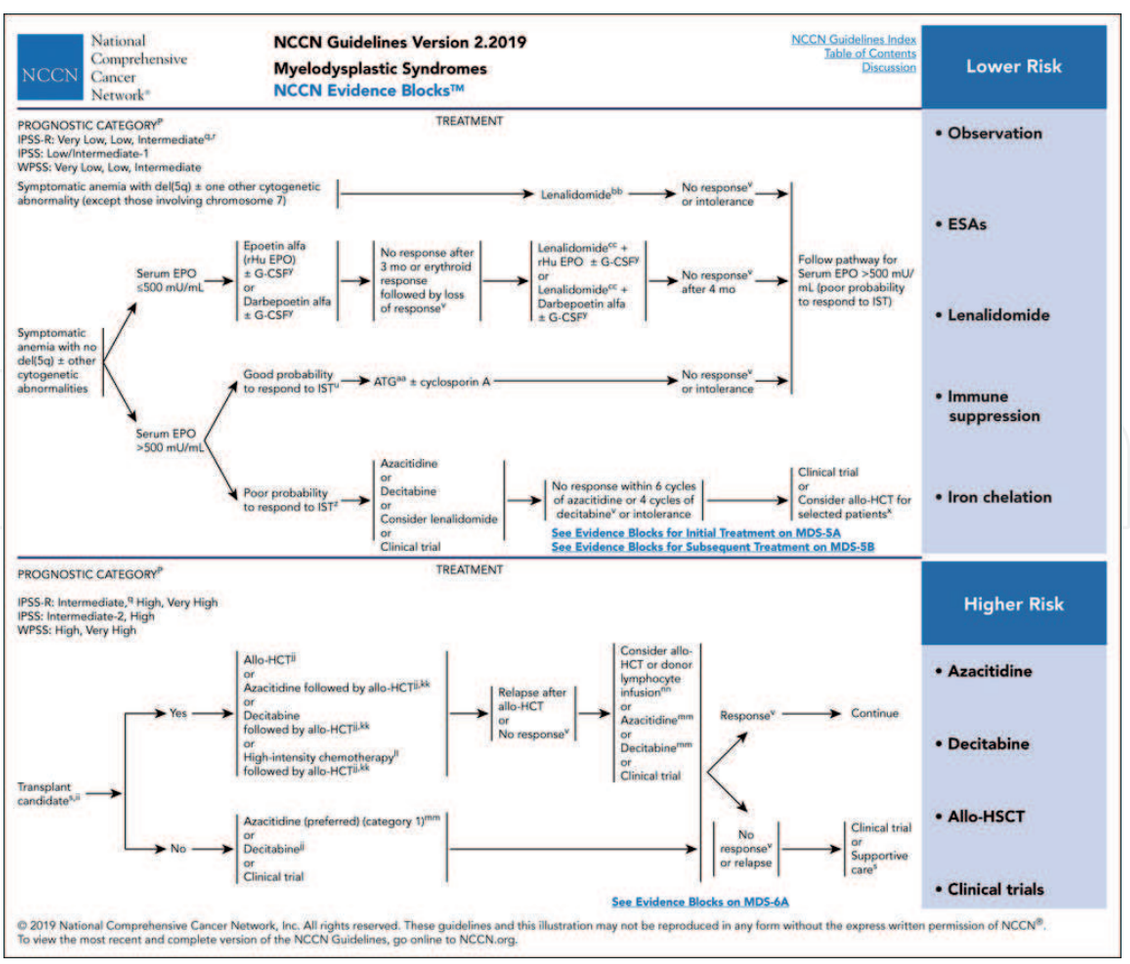

Figure 3.
The National Comprehensive Cancer Network (NCCN) guidelines stratify patients on low and high risk patient with different treatment options.

implications of specific cytogenetic abnormalities on the Revised International Prognostic Scoring System (IPSS-R). In addition, the genetic profile of a patient's disease may dictate which therapy is most appropriate (**Figure 2**).

In fact, risk stratification in the first step in the care of newly diagnosed MDS is crucial, it help to convey disease severity, can set expectations (overall survivor for months, years, or decade) and is important to define treatment strategy.

The National Comprehensive Cancer Network (NCCN) guidelines stratify patients on low and high risk patient with different treatment options (**Figure 3**).

5. Cytogenetics

Conventional prognostic scoring of MDS is based on the extent of cytopenia, the percentage of bone marrow blast infiltration, and karyotype abnormalities [8, 9].

Metaphase cytogenetic show presence of abnormalities in approximately 50% of MDS. Some of cytogenetic abnormalities are characteristic of MDS, they may be considered as specific to MDS if the clinical context is appropriate.

Only del(5q) may be considered as MDS subtype. Therefore, the 2016 revision of the WHO classification considered cases with del(5q) plus one other abnormality to be categorized as MDS with isolated del(5q), providing the second abnormality is not del(7q).

Acute myeloid leukemia (AML) is characterised by balanced abnormalities wich predominate, in contrast of MDS where unbalanced abnormalities are more common. Overall, the most frequent abnormalities are loss of the Y chromosome (-Y), del(5q), +8, del(20q), and − 7 [10, 11].

On the other hand, cytogenetic abnormalities are more frequent in therapy-related MDS (t-MDS) than de novo MDS, being reported in 70–90% cases [12].

Thus, a constitutional karyotype on a blood sample cultivated using phytohemaglutin like a mitogen can be realised in these two cases for a right interpretation of the cytogenetic response after treatment.

5.1 The deletion of 5q and "5q- syndrome"

The interstitial deletion of the long arm of chromosome 5 (del (5q)), can be considered the most frequent cytogenetic aberration in MDS, it occurs in 15% of patients with MDS. The "5q syndrome" is defined by an isolated del (5q) and an absence of excess blast, on the peripheral blood or the marrow. The IPSS includes a patient with del (5q) isolated in a favorable group. These patients have distinct morphological characteristics, thrombocytosis is found in one third of patients, macrocytic anemia and hypolobulated megakaryocytes, on the other hand, showed little dysplasia along the granulomonocytic and erythroid lines. The erythroid lineage can be hypoplastic.

The prognosis is favorable, overall survival for patients with 5q- is prolonged and the risk of progression to AML is lower than other patients with MDS. Even without treatment, clonal evolution is rarely reported. The prognosis is indeed dominated by the consequences of chronic transfusions, but these patients respond dramatically to the immunomodulating agent lenalidomide [13].

The 5q suppression can vary in size, but invariably affects bands q31 to q33. A common 5q33 deletion spanning more than 1.5 Mb and encompassing 42 genes has been reported. A model of haploinsufficiency in which the loss of a single copy of one or more genes possibly responsible for the 5q syndrome is suggested, and this may be explained by the absence of recurrent point mutation or cryptic deletion on the allele 5q normal.

5.2 Trisomy 8

Trisomy 8 + 8, (10–15%) that sometimes results from germinal mosaicism, is often subclonal, fluctuating independently of blast counts.

5.3 Monosomy 7/deletion 7q

Chromosome 7 anomalies comports del(7q), monsomy 7 (−7/del(7q)), or more rarely t(1;7), are second in frequencies after del(5q) (10%) and they have a poor Prognostic value on overall survival and risk of transformation.

Prognostic values can be possibly distinct according to regions of deletion. In fact, many and different minimal regions of deletion have been noted in 7q35–36.

Monosomy 7 can change constitutional bone marrow failures syndromes (FA, Down syndrome) or AA, or arise after radiation or toxic exposure. It is the most frequent alteration in childhood MDS where it is often associated with a degree of myeloproliferation.

Now it s known that G-CSF treatment may select a − 7 clone, and that 7q is a genetically instable region.

Patients with −7/del(7q) are characterized by neutrophil functional impairment, they are exposed to severe infections. Those patient is very have poor response to intensive chemotherapy but respond better to hypomethylating agents [14, 15].

5.4 3q26 abnormalities

The IPSS-R considers the 3q26 alterations: inv.(3)(q21q26), and t(3;3)(q21;q26) as pejorative abnormalities, they rearrange the MECOM (MDS1/EVI1) locus with complex oncogenic roles and may be accompanied by thrombocytosis. Numerous other partners of EVI1 are reported as PRDM16 in t(1;3)(p36;q21) and RUNX1 in t(3;21)(q26;q22).

5.5 17p-/-17 and TP53 mutations

Abnormalities of chromosome 17 are multiple, it can be deletion, monosomy, unbalanced translocation or isochromosome 17 which involve the loss of one TP53 locus, they are described in sMDS/AML after treatment with chemotherapy and/or radiotherapy, usually its associate with other complex genetic abnormalities.

It has been proved that chromosome 17p deletion with consistent involvement of TP53 gene located at 17p13 is associated with vacuolated pseudo-Pelger-Huet granulocytes. Those patients have poor prognosis both in MDS and AML.

5.6 Complex karyotypes

Karyotypes is considered as Complex (15%) by the presence of at least 3 anomalies that are thought to result from alterations in DNA repair or checkpoint signalling. Complex karyotypes are usully heterogeneous. The prognosis of patient having complex karyotype is worsening with each additional aberration, rather than by the chromosomes involved (most frequently, 5, 7 and 17). Complex karyotypes are by essence chemoresistant, but interesting results with the hypomethylating agent decitabine have been described by some studies.

5.7 Others abnormalities

According to the IPSS, other abnormalities can be considered as favourable:

- del(20q) which is not considered as specific of MDS, but has been related to a particularly presentation involving frequent thrombocytopenia.

- Recurrent unbalanced translocations involving 1q have been identified in primary MDS with a partial trisomy for the long arm of chromosome 1: t(1;15)(q11;p11); t(Y;1)(q12;q12), der(16) t(1;16)(q11;q11).

- secondary MDS are charactherized by translocation associated with the long arm of chromosome 7, we can also found: Deletion 9q, del(11q), del(12p) and del(13q) witch are recurrent in MDS.

- deletion of short arm of chromosome 12, del(12p) are variable. It can be associated with multiple karyotypic changes in sMDS. De novo disorders are rare with and 12p- chromosome as a sole aberration is rarely seen. Deletions are interstitial, with loss of material between band p11 and p13.

- Acquired monosomy X can be sporadically found in female MDS patients. Xq13 may also be involved in translocations in MDS, as well as in rearrangements such as an isodicentric chromosome X with breakpoint at q13 (idic (X)(q13))

Thus, chromosomal aberrations still have clinical relevance in MDS even in the era of genomic medicine. Because they basically consist in copy number changes, their detection will likely be improved by array-based karyotyping and/or by massive parallel sequencing itself [16].

6. Genetics

Novel genomic tools are now available that can both confirm clonality and provide valuable prognostic information (**Figure 4**).

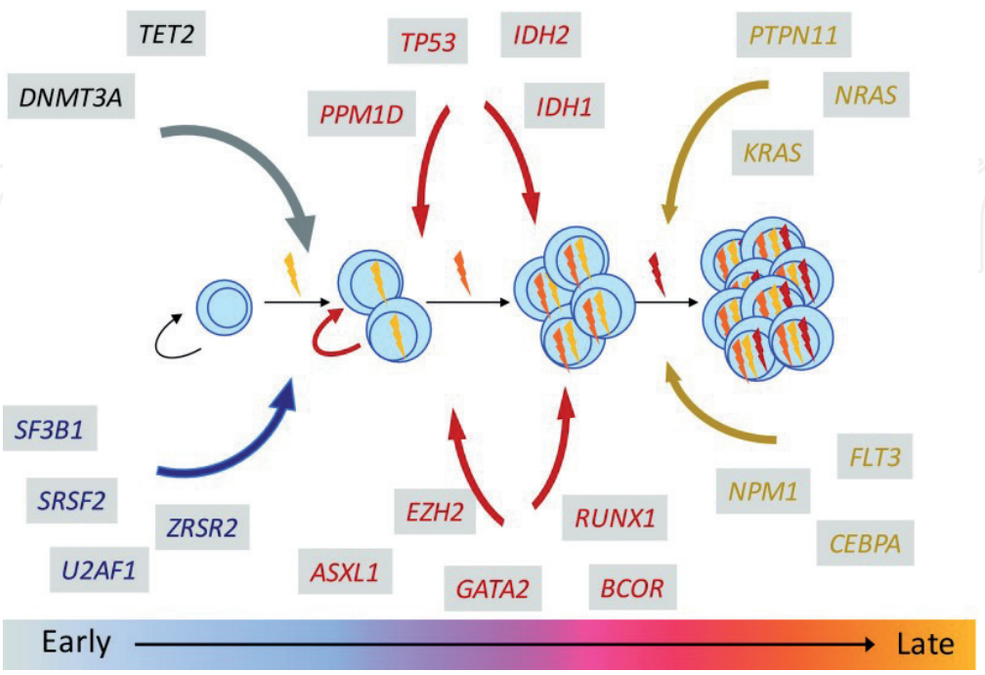

Figure 4.
Most frequently mutated pathways: serial acquisition of somaticmutations causes clonal stem cell expansion and impaired differentiation.

It is crucial to the understanding of the pathogenesis and disease phenotypes of MDS to decipher the mutations that are involved in the positive selection ("driver" mutations) and the mechanisms by which those mutations are positively selected.

Next-generation sequencing (NGS) has revealed a landscape of genetic alterations including coding exons and copy number alterations [17, 18].

The most common genetic alterations in MDS are mutations affecting RNA splicing and epigenetic modifier pathways. Those mutations are found on MDS more than AML, They are implicated on pathogenesis of MDS rather than primary AML.

Many insights have been done about the implication of these mutations on RNA splicing and the epigenome, and initial murine models of several of these mutations have been reported [19].

Mutations are frequently associated with specific disease phenotype, drug response, and clinical outcomes, and thus, it is essential to be familiar with MDS genetics for better management of patients.

MDS is typically driven by a multistep genetic process with recurrent mutations affecting basic cellular pathways, including RNA splicing, epigenome regulation, and myeloid transcriptional coordination, those abnormalities caused DNA damage and provoked stress responses, and growth factor signalling.

MDS is characterised by a lot of recurrent mutation genes and diversify of affected pathways. However, myeloid driver mutations have common fundamental biological property: they all can be responsible of clonal dominance at the stem cell level.

The diversity of clinical MDS phenotypes associated with specific mutations may be attributable to differential correlation of the hematopoietic stem cell HSC self-renewal program and lineage-specific differentiation programs.

More than 90% of MDS have somatic mutations, those mutations identify molecular pathways that drive the pathogenesis of MDS. Even low abundance mutations can have prognostic value as they identify emerging clones before they impact clinical parameters.

Among major mutational targets in MDS are the molecules involved in DNA methylations, chromatin modification, RNA splicing, transcription, signal transduction, cohesion regulation, and DNA repair.

NGS using whole-exome sequencing showed that MDS patients carry a median of 9 somatic mutations in the entire coding region, those mutations include driver mutations that advance clonal selection and passenger mutations (random mutations) that do not promote disease [20].

If we focus on the most reccurent mutated pathways, 65% of MDS patients harboured mutations in RNA splicing (SF3B1, SRSF2, U2AF1, ZRSR2) [12], followed by 47% harbouring mutations touching DNA methylation genes (DNMT3A, IDH1/2, TET2) and 28% in histone modification genes (ASXL1,BCOR, EZH2) **Figure 3** [21–23].

MDS and primary AML share common mutational targets, pleading for the same pathogenesis in different neoplasms. However, the recurrence of these mutations differed between MDS and primary AML; in MDS overrepresentation of mutations in splicing factors (SFs) and epigenetic regulators are often reported, in contrast of AML, genetic abnormalities include mutations in receptor tyrosine kinases like FLT3, RAS pathway genes, and CEBPA and IDH1/2, witch are the most frequent mutations reported [24].

Recurrent mutations are described in genes regulating DNA methylation (DNMT3A, TET2, IDH1/2), and post-translational chromatin modification (EZH2, ASXL1). Also transcription regulation (TP53, RUNX1, GATA2), are found, such as

the RNA spliceosome machinery (SF3B1, U2AF1, SRSF2, ZRSR2), cohesion complexes (STAG2), and signal transduction (JAK2, KRAS, CBL) [21].

Mutations in TP53, EZH2, ETV6, RUNX1, SRSF2 and ASXL1 occurs low survivals. [24] These mutations can predict responses treatment by hypomethylating agents and allogeneic HSCT.

Furthermore, internal tandem duplication of FLT3 (FLT3 -ITD), have been described during MDS progression and represent potential therapeutic targets [25, 26].

Therefore, a better knowledge of the molecular landscape in MDS has crucial role for determination of implications on treatment response, prognostication, and novel molecular therapeutic targeting.

Mutations in isocitrate dehydrogenase 1 or 2 (IDH1 and IDH2) are important to identify at the time of diagnosis of high- or very high-risk MDS. These particular mutations lead to abnormal leukemogenesis. Mutated IDH1 or IDH2 are not common and are only found in approximately 4–12% of patients with MDS. Those gene mutations have treatment impact. Recently, two IDH inhibitors, specifically ivosidenib targeting IDH1 and enasidenib for IDH2, are approved by the United States Food and Drug Administration (FDA) for use in AML, but not in MDS [27, 28].

Both agents are undergoing investigation in combination with azacitidine or with induction chemotherapy in patients with IDH-mutant MDS.

Other mutations are very important to identify early because of their prognostic impact, like SF3B1 mutations, in fact mutations of SF3B1 are strongly associated with ring sederoblasts, and a typical SF3B1 can be presumptive evidence of MDS, and have more favorable prognosis [29].

More than third of MDS patients with less than 5% of blasts will have an adverse gene mutation. These include mutations cited before like SRSF2, U2AF1, ASXL1, RUNX1, EZH1, TP53, IDH1, NRAS, and PRPF8, but the only mutation having good prognosis is SF3B1 mutation [30].

For patient with MDS and having more than 5% of blasts (5–30% blasts), several mutated genes retain their in higher risk MDS. In fact, mutation of TP53, CBL, RUNX1, PRPF8 are utch more common and remain adverse, and SF3B1 mutation are rare end no longer favourable.

Somatic mutations alone are not great predictors of outcomes after treatment with approved MDS therapies, but mutations of TP53 and epigenic regulators like TET2 and DNMT3A have shown associations with response to hypomethylating drugs in some studies. In contrast of that, we do have a cytogenical marker there is very good for predictive response to therapy: it s about Del (5q) and lenalidomide. In fact patient having Del(5q) can response favourably to lenalidomide, if TP53 mutations are absents, because TP53 mutations indicate resistance to lenalidomide and predict relapse or progression even after allogeneic stem cell transplantation.

Data are accumulating to support use of next-generation sequencing (NGS) in the diagnosis and management of patients with MDS.

The treatment and management of older patients with MDS is extremely challenging due to a number of reasons, including advanced disease, intolerability to therapy, significant comorbidities, and potential for more drug–drug interactions with concomitant therapy.

7. Conclusion

Our knowledge about the genetics of myelodysplastic syndromes (MDS) and related myeloid disorders has been dramatically improved during the past decade, in which revolutionized sequencing technologies have played a major role.

Cytogenetic abnormalities have extensive utility in MDS, they have many implications for diagnosis and prognosis. The best example is represented by MDS with isolated del(5q). the presence of del(5q) is known to be a lenalidomide-responsive condition with a clearly elucidated molecular mechanism.

The use of additional genomic information, provided by DNA microarrays and sequencing, holds great promise in further refining the classification and management of these disorders.

At present, NGS is rarely incorporated into clinical guidelines although an increasing number of studies have demonstrated the benefit of using NGS in the clinical management of MDS patients [31].

Conflict of interest

Authors declare have no conflict of interest.

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