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Review

Classification of myelodysplastic syndromes 2015

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Abstract

The Myelodysplastic syndromes are a heterogeneous group of hematological malignancies difficult to diagnose and classify, for which novel treatments are beginning to emerge. Recent advance in diagnosis classification, prognosis scoring and genetics discovery are presented in this update.

Keywords

Myelodysplastic syndromes; Refractory Anemia with excess blasts; Refractory Anemia with Ring sideroblasts; Refractory Cytopenia with Unilineage Dysplasia; Refractory Cytopenia with Multilineage Dysplasia; MDS-Unclassifiable; Thrombocytopenia; Neutropenia; Anemia

Note

This paper is an update of " Classification of myelodysplasic syndromes 1999 " (Flandrin, 2002).

Clinics and pathology

Disease

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of the hematopoietic stem cell (HSC) characterized by peripheral cytopenias despite increased hematopoïetic precursors, leading to transformation into acute myeloid leukemia (AML) in 20-30% of cases (Mufti, 2004).

Clinical manifestations result from cytopenias (anemia, infection, and bleeding). Diagnosis is based on blood cytopenias and hypercellular bone marrow (BM) with dysplasia, with or without excess of blasts.

Phenotype/cell stem origin

MDS is thought to result from the accumulation of genetic or epigenetic (such as promoter hypermethylation) lesions, occurring initially in an immature progenitor and leading to a proliferative advantage of the MDS clone over normal immature progenitors. MDS progenitors display abnormal terminal differentiation and increased susceptibility to apoptosis. These two features explain the clinical consequences of blast accumulation and peripheral cytopenias (Mufti, 2004).

Etiology

Age-induced genetic, epigenetic, and immune-mediated changes in haemopoietic stem cells (HSC) lead to oligoclonal expansion of myelodysplastic stem cells, with defective differentiation, characterised by increased apoptosis of erythroid and myeloid progenitors (Corey et al., 2007). Microenvironmental changes and immune deregulation contribute to this differentiation defect. Congenital bone marrow failure syndromes as Fanconi's anemia (FA), neurofibromatosis, dyskeratosis, Down syndrome and familial platelet disorder (associated with germ line mutations of RUNX1 or CEBPa) predispose to MDS/ AML.

Epidemiology

The median age at diagnosis is approximately 70 years.

Subtype	Blood	Marrow
Refractory Anemia with excess blasts 1 (**RAEB-I**)	Cytopenia (s) <5% Blasts No auer rods <1 G/L Monocytes	Unilineage or multilineage dysplasia No Auer rods 5-9% Blasts
Refractory with anemia With excess blasts II (**RAEB II**)	Cytopenia(s) 5-19% blasts Auer rods possible <1 G/L Monocytes	Unilineage or multilineage dysplasia 10-19% Blasts Auer rods possible
Refractory Cytopenia with Unilineage Dysplasia (**RCUD**) Uni-or Bicytopenia Refractory Thrombocytopenia (**RT**) Refractory Neutropenia (**RN**) Refractory Anemia (**RA**)	Anemia No Blasts	Only one cytopenia with dysplasia in >10% cells <5%Blasts <15% Ring sideroblasts
Refractory Anemia with Ring sideroblasts ID: 1 1106 > (**RARS**)	Anemia No blasts	Dyserythropoiesis only < 5% Blasts >15% Ring sideroblasts
Refractory Cytopenia with Multilineage Dysplasia with or without Ring sideroblasts (**RCMD**)	Cytopenia (s) = 1% blasts No Auer rods. <1 G/L Monocytes	Dysplasia in >10% of the cells of 2 cell lines < 5% Blasts, no Auer rods. 15% Ring sideroblasts
MDS with isolated del (5q)	Anemia Normal or elevated platelets = 1% blasts	5% blasts, no Auer rods Hypolobulated megakaryocytes
(MDS-U)	Cytopenia = 1% blasts	Dysplasia in < 10% cells but cytogenetic abnormality considered as presumptive for MDS < 5% blasts

Table 1: WHO classification for MDS (Vardiman et al. 2009)

The incidence is 4 to 5 per 100,000 persons per year. The etiology is generally unknown, the role of exposure to environmental chemical and physical mutagens is sometimes suspected. In 15 to 20% of cases, however, MDS are secondary (sMDS) to chemotherapy and/or radiotherapy for a prior illness, usually cancer. More rarely, they are secondary to exposure to benzene or other aromatic hydrocarbons, or products used in agriculture.

Cytology

MDS have received a variety of nomenclatures, until the first international classification by the French American British (FAB) group in 1982 (Bennett et al., 1982). This classification has been refined in 2001 then in 2008 by a WHO expert committee (Vardiman et al, 2002; and 2009), integrating novel prognostic factors in MDS, such as multilineage dysplasia. The marrow blast threshold of AML was lowered from 30% to 20%. This classification also designed the term MDS/MPN (Myeloproliferative Neoplasm) to regroup a heterogeneous set of rare entities including chronic myelomonocytic leukemia (CMML), previously considered as a MDS.

Three minimal criteria must be met for the diagnosis of MDS: 1) persistent (> 6 months) and significant cytopenia(s) (Hb < 10 g/dL, absolute neutrophil count < 1.8 G/L, platelets < 100 G/L), 2) significant bone marrow dysplasia, or blast excess or typical cytogenetic abnormality, and 3) exclusion of differential diagnoses (Kaloutsi V et al., 1994;Bennett et al., 2009).

Presence of dysplasia is the first key criterion for diagnosis and prognosis of MDS.

A given lineage is considered dysplastic if two or more dysplastic features are found on > 10% cells. Multilineage dysplasia (MD) is defined as the coexistence of dysplasias in two or more lineages. Blast excess is frequent in MD but 40-60% of cases occur without blast excess.

The term idiopathic cytopenias of undetermined signification (ICUS) has been coined to account for cases when differential diagnoses have been excluded, but cytopenias or dysplasias do not reach significant MDS diagnostic thresholds. The outcome of ICUS still remains undetermined, but probably evolves sometimes into MDS, and thus requires blood and BM monitoring (Wimazal et al., 2007).

Ringed sideroblasts (RS), ie. sideroblasts with ? 5 siderophilic granules contouring at least a third of the nucleus circumference, are not specific of MDS as they can be encountered in a variety of conditions such as alcohol consumption, copper deficiency or zinc excess, as well as a rare congenital condition called X recessive sideroblastic anemia. RS are considered significant when they represent > 15% of erythroid cells. However, in the absence of blast excess, RS define an entity with favourable prognosis, termed refractory anemia with ringed sideroblasts (RARS).

	Proportion of patients (%)	Karyotype	Median survival (years)	Time to 25% AML evolution (years)
Very good	4%	-Y, del(11q)	5.4	NR
Good	72%	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4
Intermediate	13%	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor	4%	-7, inv(3)/t(3q)/del(3q) double including -7/ del(7q) Complex: 3 abnormalities	1.5	1.7
Very poor	7%	Complex > 3 abnormalities	0.7	0.7

Table 2a: Karyotype (IPSS-R) - AML =acute myeloid leukaemia. NR = not reached.

Auer rods have historically been recognized as a poor prognostic marker and remain considered in the WHO classification.

Some morphologies can be strongly evocative of a precise underlying cytogenetic or genetic aberration. For instance, a characteristic dysgranulopoiesis combining pseudo-Pelger-Huüt anomaly and small vacuolated neutrophils has been associated with 17p deletions and TP53 tumour suppressor gene mutations (Lai et al., 1995). The "5q- syndrome" which was recognized in 2001 by the WHO classifications also has a distinct morphology.

Precise count of BM blasts is the second central criterion for diagnostic and prognostic classification of MDS. Myeloblasts are consensually defined by a high nuclear/cytoplasmic ratio and diffuse chromatin pattern, can be "agranular" or "granular". A third class of blasts defined by the presence of numerous (>20) azurophilic granules is included in the blast percentage, and can be distinguished from promyelocytes by the lack of Golgi structure (Mufti et al., 2008)

Pathology

BM biopsy first allows objective evaluation of BM cellularity, which physiologically declines with age. Application of a standardized age correction to cellularity brings the incidence of "hypoplastic" MDS from 29% to 7% (Thiele et al., 2005). Hypoplastic MDS raises the question of the differential diagnosis with aplastic anemia (AA). Features of MDS are the presence of circulating myeloblasts, megakaryocytic or granulocytic dysplasia. Mild erythroid dysplasia can be seen in AA. Other MDS criteria include abnormal sideroblasts, presence of two or more blast cell clusters. Clusters (3-5 cells) or aggregates (> 5 cells) of blasts cells away from endosteal or vascular niches, in the central portion of the BM, have been dubbed "abnormally localized immature myeloid progenitors" (ALIP). ALIP have been proposed as diagnostic and prognostic markers.

Immunohistochemistry with a CD34 antibody marks immature hematopoietic progenitors and megakaryocytes, and can be used to asses the blast percentage.

However, some MDS have CD34- blasts in MDS: in those cases, CD117 has been proposed as a surrogate marker.

Some authors have proposed that the presence of CD34+ cell clusters may better reflect prognosis than CD34+ cell percentage.

Treatment

Treatment varies from symptomatic treatment of cytopenias, especially by transfusions for anemia, to allogeneic stem-cell transplantation. Treatment of patients with lower-risk myelodysplastic syndromes includes growth factors and lenalidomide. Higher-risk patients are treated with hypomethylating agents and, allogeneic stem-cell transplantation whenever possible (Fenaux et al. 2009).

Evolution

Progression to acute myeloid leukaemia depends on prognosis factors. Rare cases progress to aplastic anemia.

Prognosis

Prognostic evaluation in MDS still largely relies on an International Prognostic Scoring System (IPSS) established on the basis of an international cohort of patients (IMRAW cohort) treated symptomatically and recently revised (IPSS-R) (Greenberg et al, 1997; and 2012). IPSS relies on number of cytopenias, marrow blast percentage and cytogenetic. Patients are regrouped into four risk categories (low, intermediate 1 and 2, and high).

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM blasts (%)	=2%		> 2-< 5%	5-10%	5-10%	> 10%	
Hemoglobin (g/dL)	=10		8 < 10	> 8			
Platelets (G/L)	=100	50 < 100	< 50				
ANCs (G/L)	=0,	< 0.8					

Table 2b: IPSS-R Prognostic Score Values - ANC: Absolute neutrophil count, BM: bone marrow

RISK GROUP	RISK SCORE
Very low	=1. 5
Low	> 1.5 - 3
Intermediate	> 3 - 4.5
High	> 4.5 - 6
Very High	> 6

Table 2 c: IPSS-R Prognostic risk Categories/Scores

The IPSS has since been validated in many therapeutic contexts including intensive chemotherapy and allogeneic stem cell transplantation (ASCT). IPSS categories are often regrouped into lower-risk MDS (IPSS low and intermediate-1), and higher-risk MDS (IPSS intermediate-2 and high). Lower-risk MDS are patients with prolonged survival where the main objectives are to cope with chronic cytopenias notably anaemia, and to defer ASCT. On the other hand the treatment in higher-risk MDS should alter disease history and prolong survival. The approval of azacytidine in higher-risk underscores the importance of IPSS evaluation in all patients at diagnosis.

According to the IPSS-R, 27% of the lower-risk MDS patients of the original IPSS are reclassified as having a higher risk and they potentially need a more intensive treatment. Conversely18% of high-risk MDS patients, as defined by the original IPSS, are reclassified as low risk by the IPSS-R.

Genetics

Clonality assays based on gene imprinting (HUMARA assays) have historically been the first molecular tools to confirm the clonal nature of normal karyotype MDS. They still can serve as diagnostic co-criterion, but novel genomic tools are now available that can both confirm clonality and provide valuable prognostic information. (Bejar R et al 2011)

Cytogenetics

Cytogenetics morphological

Conventional cytogenetic in de novo MDS is abnormal in 35-40% of patients by conventional banding karyotyping, and cytogenetic aberrations are highly heterogeneous.

Abnormal karyotype, especially those of unfavourable prognosis, are more frequent in cases with blast excess, with 75% RA presenting with Normal karyotype (NK), compared to 25-50% abnormal karyotype in RAEB1-2, or secondary MDS (80% versus 40% in de novo MDS).

The most frequent types of abnormalities by frequency order are total or partial chromosome losses, total or partial chromosome gains, and unbalanced translocations. Balanced translocations are rare.

Frequent alterations represent 40% of all abnormal karyotypes, including partial or total deletion of chromosome 5 (?5/5q?), partial or total deletion of chromosome 7 (-7/del(7q)), trisomy 8 (+8), partial deletion of chromosome 20 (del(20q)), and Y chromosome loss (?Y). These last alterations are not specific of MDS and can be encountered in AML or in myeloproliferative neoplasm. Loss of chromosome Y can be found in elderly healthy subjects (Wiktor et al, 2000). Trisomy 8 and loss of Y may be present in a constitutional mosaicism. Thus a constitutional karyotype on blood sample cultivated with phytohemaglutin as mitogen can be performed in those two cases for correct interpretation of cytogenetic response after intensive therapy or transplantation.

Chromosome 5 and 7 alterations and other infrequent alterations in AML are considered as "myelodysplasia related changes" in the current WHO classification, as they may reflect an underlying undiagnosed myelodysplasia. The remaining 60% of abnormal karyotype display rare alterations

Del5q and the "5q- syndrome"

Interstitial deletion of the long arm of chromosome 5 (del(5q)), is the most frequent cytogenetic aberration in MDS, occurring in 15% of patients. The "5q- syndrome" first described by Van den Berghe in 1974, is characterized by an isolated del(5q) and absence of PB or BM blast excess, and is now part of WHO classifications (Vardiman et al, 2008). Isolated del(5q) is favourable in the IPSS. The distinct morphologic features of 5q- syndrome include thrombocytosis in a third of patients, macrocytic anemia, and hypolobulated megakaryocytes, contrasting with little dysplasia along the granulomonocytic and erythroid lineages. The erythroid lineage may often be hypoplastic. Prognosis is favourable, with a prolonged overall survival and a low risk of progression to AML. Clonal evolution is also rare without treatment. The prognosis is in fact dominated by the consequences of chronic transfusions, but these patients dramatically respond to the immunomodulatory agent lenalidomide, with two thirds reaching long-term transfusion independency (Raza et al, 2008).

The 5q deletion is variable in size, but invariably affects the q31 to q33 bands. A common 5q33 deletion spanning over 1.5 Mb and encompassing 42 genes has been delineated. The lack of recurrent point mutation or of cryptic deletion on the normal 5q allele supports an haploinsufficiency model whereby loss of a single copy of one or more probably several genes cause 5q syndrome. Several candidate genes have been implicated including SPARC, CTNNA1, EGR1, and RPS14. Haploinsufficiency for the ribosomal subunit RPS14 induces a P53-dependent block in erythroid proliferation and differentiation, whereas haploinsufficiency of two micro-RNAs, MIR145 and MIR146a, leads to dysmegakaryopoiesis and thrombocytosis (Ebert et al, 2008).

Patients with blast excess or additional cytogenetic aberrations can also harbour del(5q) but the prognosis is much more unfavourable than 5q-syndromes.

Trisomy 8

Trisomy 8 +8, (10-15%) that sometimes results from germinal mosaicism, is often subclonal, fluctuating independently of blast counts. This suggests it is a secondary lesion in MDS.

Monosomy 7 / deletion 7q

Chromosome 7 anomalies including del(7q), monsomy 7 (-7/del(7q)), or more rarely t(1;7), are second in frequencies after del(5q) (10%) and have almost invariably been assigned a poor prognostic value in terms of both survival and transformation risk. Different minimal regions of deletion have been described in 7q35-36, possibly with distinct prognostic values. Monosomy 7 can transform 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 accompanied by a degree of myeloproliferation. There also is in vitro evidence that G-CSF treatment may select a -7 clone, and that 7q is a genetically instable region. Patients with -7/del(7q) have neutrophil functional impairment, and thus may present severe infections despite moderate neutropenia.

Those patients poorly respond to intensive chemotherapy but interesting results have been described with ypomethylating agents (Fenaux et al., 2009).

3q26 abnormalities

Other reputed pejorative abnormalities considered in the IPSS-R include the 3q26 alterations inv(3)(q21q26), and t(3;3)(q21;q26) that rearrange the MECOM (MDS1/EVI1) locus with complex oncogenic roles and may be associated with thrombocytosis. Numerous other partners of EVI1 are known as PRDM16 in t(1;3)(p36;q21) and RUNX1 in t(3;21)(q26;q22).

17p- / -17 and TP53 mutations

17p deletion, monosomy 17, unbalanced translocation or isochromosome 17 which involve the loss of one TP53 locus are found mainly in sMDS/AML after chemotherapy and/or radiotherapy, usually in association with other complex chromosomal anomalies. There is an association between vacuolated pseudo-Pelger-Huet granulocytes and chromosome 17p deletion with consistent involvement of TP53 gene located at 17p13. It occurs in MDS and AML with poor prognosis. Some reports pinpoint the strong association of TP53 mutations and 5q deletion in MDS (Jädersten et al, 2011).

Others abnormalities

Other favourable aberrations in the IPSS include del(20q) which is not specific of MDS, and has been associated with a specific presentation involving frequent thrombocytopenia.

Recurrent unbalanced translocations involving 1q have been found in primary MDS with a partial trisomy for the long arm of chromosome 1. Such rearrangements are described as t(1;15)(q11;p11); t(Y;1)(q12;q12), der(16) t(1;16)(q11;q11). In secondary MDS translocation with the long arm of chromosome 7 is not rare.

Deletion 9q, del(11q), del(12p) and del(13q) are recurrent in MDS. MDS presenting with deletion of the short arm of chromosome 12, del(12p) are heterogeneous. Association with multiple karyotypic changes in sMDS is more common than de novo disorders with a 12p- chromosome as a sole aberration. Deletions are usually interstitial, with loss of material between band p11 and p13. FISH method has been used to show that both ETV6 and the gene for an inhibitor of a G1 cyclin-dependant protein kinase (CDKN1B) are deleted in all myeloid

malignancies with a del(12p) including MDS (Haferlach et al, 2011).
Acquired monosomy X has been 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)).

Complex karyotypes

Complex karyotypes (15%) are conventionally defined as the coexistence of at least 3 anomalies that are thought to result from alterations in DNA repair or checkpoint signalling. Complex karyotypes are by essence heterogeneous, with a prognosis worsening with each additional aberration, rather than by the chromosomes involved (most frequently, 5, 7 and 17). Complex karyotypes are highly chemoresistant, but interesting results with the hypomethylating agent decitabine have been observed, that need to be confirmed on larger cohorts.

Rare translocations

t(2;11)(p21;q23) implicate miR-125b1;t(6;9)(p22;q34) leads to DEK/NUP214 fusion.

Clonal evolution

New rearrangements frequently occur, with disease progression. Limited data is available on the prognostic value of clonal evolution, but it is generally considered pejorative, as higher-risk aberrations appear.

Genes involved and proteins

Note

Somatic mutations are observed in approximately 80% of the MDS (Bejar et al, 2011). The most common genes are those involved in epigenetic regulation (TET2 , ASXL1, EZH2, DNMT3A, IDH1, IDH2 (Kosmider et al, 2009), splicing (SF3B1, correlated to RARS, SRSF2, U2AF35, ZRSR2)(Damm et al, 2012), transcription (RUNX1 , ETV6, CBL, NRAS , KRAS, NF1, PTPN1, TP53) and less often cohesin genes. TP53 mutated subclones may occur at early disease stage in MDS with del(5q) where they are associated with a lower response to lenalidomid and an increases risk of progression. (Jädersten et al, 2011).
It has recently been described that approximately half of RARS with thrombocytosis (RARS-T) patients, along with a small subset of other MDS and mixed myelodysplastic/ myeloproliferative disorders, carry the JAK2 ^{V617F} mutation, and scarcely MPL mutations. RARS-T patients show clinical features of both RARS, essential thrombocytemia and to some extent myelofibrosis. However, the degree of anaemia and overall survival is more similar to RARS than to myeloproliferative disorders (Hellström-Lindberg et al., 2008)

Over expression of the EVI1 gene is found in one third of MDS patients, particularly those with blast excess, even without 3q26 rearrangement in conventional cytogenetic.
As in AML, the WT1 transcription factor is also over expressed in virtually all cases of MDS with blast excess, but also in a third of lower-risk MDS. The leukemogenic potential of this lesion is still unclear, but its over expression can provide a tool for minimal residual disease (MRD) monitoring in the context of intensive therapy, like in AML.

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