Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Perspective

Current and Proposed Classification Criterion and Prognostic Models for the Myelodysplastic Syndromes and Dysplastic Cytopenias of Undetermined Significance

Steven Sandler*
Department of Oncology, North Shore University Health Systems, USA

***Corresponding author:** Steven Sandler, Department of Oncology, North Shore University Health Systems, 9669 N. Kenton Ave. Suite 510, Skokie, Ilinois 60076, USA

Received: April 27, 2016; **Accepted:** June 13, 2016; **Published:** June 15, 2016

Abstract

Myelodysplastic syndromes (MDS) are a heterogeneous group of closely related clonal disorders. They are characterized by one or more peripheral blood cytopenias and a bone marrow that shows < 20 percent blasts and >10 percent dysplasia of one or more of the marrow cell lines. Approximately 20-30 percent of MDS patients will progress to acute myeloid leukemia. Like other malignancies, MDS involves the stepwise acquisition of driver mutations. Traditionally, conventional cytogenetics and FISH have identified a clonal mutation in about 30-50 percent of patients. Using next generation sequencing, driver mutations have been identified in up to 90 percent of MDS patients. The most commonly mutated genes include somatic mutations in the SF3BI spliceosomal gene which is seen in 60-80 percent of patients with refractory anemia with ringed sideroblasts. Epigenetic mutations are seen in TET2, DNMT3A, IDH 1&2, E2H2, ASXLI, transcription factor mutations are seen in RUNXI and ETV6 and tumor suppressor genes are found such as TP53. There is also a new understanding of hematological entities that are characterized by cytopenias, but do not fit the criteria of MDS. Idiopathic cytopenia of undetermined significance (ICUS) is recognized by hematological cytopenias and dysplasia may be present, but is minimal (< 10%). Clonal cytopenias of undetermined significance (CCUS) is recognized when both cytopenias are present and clonal mutations are found, however the WHO classification criteria for MDS are not present. It has also been recognized that somatic genetic mutations associated with MDS increase steadily with age. The entity of clonal hematopoiesis of indeterminate potential (CHIP) refers to usually older patients with clonal mutations, detectable at a variant frequency of ≥2%, but may have no hematological abnormality. Similar to monoclonal gammopathy of undetermined significance and monoclonal B-cell lymphocytosis, CHIP converts to a hematological malignancy at a rate of 0.5-1% per year.

Perspective

Myelodysplastic (MDS) syndromes define a group of hematological disorders whose pathological findings have been well defined [1]. Controversy exists, however in the reproducibility of the various subtypes. The 4th edition of the World Health Organization (WHO) classification of tumours of the Hematopoietic and Lymphoid Tissues was last published in 2008 [2,3]. The classification included morphology, clinical parameters, immunophenotyping and genetics. The 5th edition is expected in 2016 and proposed changes will be discussed in this article.

The foundation for the diagnosis of MDS relies on the morphological dysplasia involving one or more cell lines and ineffective clonal hematopoiesis those results in peripheral blood cytopenias. The MDS syndromes are inherently volatile and can transform to acute myeloid leukemia [4]. In current terminology, MDS patients are defined by cytopenia (s): median hemoglobin < 11g/dl and 80% have an absolute neutrophil count < 1.0 x 10^9/L or platelets <100 x 10^9/L. In addition, there must be less than 20% myeloblasts in the bone marrow, >10% dysplasia in one or more of the lineages, evidence of clonality and/or an abnormal karyotype typical for MDS [5]. Even among expert pathologists, there has been inter-observer variation and there can be difficulty in distinguishing MDS from non-neoplasticS disorders [6]. One must exclude Vitamin B12 and folate deficiency, HIV or other infection, alcohol abuse, medications such as methotrexate and chemotherapy, copper deficiency, autoimmune disorders such as ITP, LGL disorders, Fanconi's anemia and even aplastic anemia and myeloproliferative disorders [7]. The clonal dysplastic features of the hematopoietic cell lines are essential to the WHO definition of MDS. However, except with MDS associated with isolated 5(delq), the diagnosis of MDS has not yet been established by chromosomal abnormalities or discrete gene abnormalities, since most of the chromosomal abnormalities and/or discrete genetic lesions are not specific to a diagnosis of MDS (i.e., can be seen in AML and even non-myeloid malignancies) and therefore the use of these modalities to confirm a diagnosis of MDS is unreliable [8].

MDS is classified in the bone marrow by first obtaining a well-stained bone marrow aspirate. According to the WHO (2008) criteria, 500 cells should be counted. Although not specific to MDS, the current classification paradigm includes >10% of a hematopoietic cell line as dysplastic. Common findings in the morphology include

Citation: Sandler S. Current and Proposed Classification Criterion and Prognostic Models for the Myelodysplastic Syndromes and Dysplastic Cytopenias of Undetermined Significance. Ann Hematol Oncol. 2016; 3(3): 1084.

neutrophil hypogranularity, erythroid abnormalities that include an altered nuclear: cytoplasmic ratio. Nuclear budding, bilobed nuclei, cytoplasmic vacuoles and small hypolobulated megakaryocytes [9]. The morphology will not change in the WHO (2016) revision, however the nomenclature will change. The terms refractory anemia and refractory cytopenia will be replaced by MDS [10]. Currently MDS with isolated del (5q) is the only MDS entity defined by a cytogenetic abnormality [11].

Conventional cytogenetics are included as an obligatory prerequisite for the evaluation and prognosis of suspected MDS [12-14]. Using conventional cytogenetic techniques, about 50% of de novo MDS patients will be found to have a chromosomal abnormality. There is an inverse correlation between the number of chromosomal abnormalities and the median survival. By expanding the data base, additional cytogenetic abnormalities were incorporated into the IPSS-R. Schanz, et al. developed a cytogenetic classification scoring system based on 2902 untreated, de novo MDS patients [15]. The MDS syndrome characterized by del (5q) is known to have a favorable prognosis and a high response to Lenalidomide [16]. Even the addition of one additional chromosomal abnormality (except monosomy 7) does not affect survival; however ≥2 chromosomal abnormalities will markedly reduce survival from 58 months to 6.8 months [17].

Fluorescence in situ hybridization (FISH) is a cytogenetic technique that use fluorescent probes that only bind to those parts of the chromosome with a high degree of complementarity [16]. It is used to detect and localize the presence or absence of specific chromosomal translocations and gains and losses of DNA segments that are commonly found in MDS. FISH can be used on non-dividing cells and even used in identifying and risk stratifying chromosomal abnormalities in the peripheral blood, when a bone marrow is not obtainable. FISH does not appear to add a significant amount of information to conventional cytogenetics [18]. The relevance of small clones detected only by FISH and not karyotyping is not established. Flow cytometry immunophenotyping will probably not be required in the WHO (2016) revision; however it may provide useful information in difficult cases. A CD34+ count is relevant in high-risk disease. If the information is relevant, it should become part of the final report [19].

MDS with ringed sideroblasts with single lineage dysplasia (MDS-RSSLD) or multi lineage dysplasia (MDS-RSMLD) represents a significant change in the proposed WHO (2016) revision [10]. The percentage of ringed sideroblasts does not correlate with prognosis [20]. In the WHO (2008) classification, there was refractory anemia with ringed sideroblasts (RARS) and the category refractory anemia with multi lineage dysplasia with ringed sideroblasts (RCMD-RS) was incorporated into the category of refractory cytopenia with multi lineage dysplasia (RCMD), since the prognosis of RCMD was similar to RCMD-RS [21]. Mutations in the spliceosome of gene SF3B1 has been strongly associated with ringed sideroblasts [22,23]. Since RARS and RCMD-RS express the SF3B1 gene mutation, share a unique gene expression profile and show ringed sideroblasts, the WHO (2016) proposed classification will retain the WHO (2008) category on RARS, but now called MDS-RSSLD and the new category of MDS-RSMLD [10]. Ringed sideroblasts are not unique to MDS and can be seen refractory anemia with excess blasts and even in AML, however these entities are defined by their blast counts [24]. The identification of the SF3B1 gene mutation, when present will allow the diagnosis of MDS-RSSLD or MDS-RSMLD when ringed sideroblasts are present, but less than 15% [10]. The SF3B1 gene mutation will not be required for diagnosis, however in patients found to have > 5% ringed sideroblasts but < 15%, the presence of this mutation will still identify a distinct subset of myelodysplastic syndrome with ringed sideroblasts.

MDS, unclassified is characterized by cytopenias and < 1% blasts in the peripheral blood, unequivocal dysplasia < 10% of the cells and presumptive evidence of a cytogenetic abnormality considered as presumptive evidence of a diagnosis of MDS and < 5% blasts.

Current WHO (2008) classification for MDS

Refractory anemia

Refractory neutropenia

Refractory thrombocytopenia

Refractory anemia with ringed sideroblasts

MDS associated with isolated del (5q)

Refractory cytopenia with multi lineage dysplasia

Refractory anemia with multi lineage dysplasia with ringed sideroblasts

Refractory anemia with excess blasts-1

Refractory anemia with excess blasts-2

MDS, unclassified

Proposed WHO (2016) classification for MDS

MDS with single-lineage dysplasia (MDS-SLD)

MDS with multi lineage dysplasia (MDS-MLD)

MDS with single lineage dysplasia and ringed sideroblasts (MDS-RSSLD)

MDS with multi lineage dysplasia and ringed sideroblasts (MDS-RSMLD)

MDS with excess blasts-1 (MDS-EB1)

MDS with excess blasts-2 (MDS-EB2)

MDS, unclassified

Erythroleukemia (erythroid/myeloid type) was defined in WHO (2008) as having at least 50% erythroid precursors in the entire marrow nucleated cell population and myeloblasts that account for at least 20% of the non-erythroid cell population. There has to be >20% myeloblasts in the total non-erythroid cell population [25]. This has caused confusion because you can still have a high number of erythroid precursors and a low total bone marrow myeloblast count and still allow the diagnosis of acute leukemia [26]. The erythroid/myeloid type of acute erythroid leukemia has been divided into different prognostic subsets based on their cytogenetic and molecular genetic features [27]. In the WHO (2016) edition, it has been proposed that the non-erythroid blast count criteria be eliminated

from erythroleukemia of the myeloid/erythroid type and if the total myeloid blast count is < 20%, the case is classified into the proper MDS category. Acute erythroleukemia will remain a subtype of acute myeloid leukemia in the WHO (2016) proposal.

The natural history of MDS varies considerably between individuals which correlate with the mosaic of subtypes of MDS [28]. Some patients live months, while other live years. There are three FDA approved agents for the treatment of MDS, 5-Azacytidine, Decitabine and Lenalidomide. Immunosuppressive medications and allogeneic stem cell transplantation are also used. One of the greatest challenges with our current therapeutics is to balance the current therapeutic benefit of treatment with the associated toxicities of treatment. Designing models to accurately predict an individual's survival is predominant and essential to guide the proper timing and selection of the therapeutic.

Current models for risk stratification were limited by information that could be obtained from examination of the complete blood count, the examination of the bone marrow and conventional cytogenetics. The 1997 International Prognostic Scoring System (IPSS) is still used as a standard prognostic tool in clinical trials [29]. The prognosis relied on the sum of three components: the blast count, the karyotype and the number of peripheral blood cytopenias to calculate a score. The score stratifies patients into risk groups which are correlated with their overall survival. The higher the score, the shorter the survival. There are 4 assigned risk groups: lower risk MDS included low risk and INT-1 and high risk included INT-2 and high risk, based on the scoring system. This type of scoring system was used in subsequent models to estimate an individual's expected survival. This first attempt at a classification scheme for MDS had several deficiencies that led to other models [30]. Specifically, there was a limited number of karyotypes, transfusion dependence was not included, prior therapy, the degree of cytopenias and the spectrum of dysplasia was not considered and patient's with CMML/MPN or T-MDS were not included. The IPSS included a category of 20-30% blasts, which have now been reclassified as AML with myelodysplastic features. The model only included newly diagnosed patients with MDS. A revised IPSS (IPSS-R) was published in 2012 [31]. The IPSS-R included more prognostic karyotypes, included the percentage of blasts, the hemoglobin, platelet count and the ANC. In the IPSS-R scoring system, more significance was given to the cytogenetics than in the IPSS.

While the three essential elements of the IPSS, the bone marrow blast percentage, cytogenetics and cytopenias, the definition and scoring of each category was refined. The bone marrow blast percentage of ≤ 5% was divided, certifying that even a small number of blasts in the circulation were an adverse risk factor. The cytogenetic stratification allowed for more proportional influence than in the IPSS. The degree of a cytopenia was more relevant than just an affected cell lineage. The categories were calculated into the very low, low, intermediate, high and very high risk groups. Both the IPSS and the IPSS-R calculated the median survival time for 25% of the patients to transform to AML.

Because of the wide variation in each IPSS and IPSS-R group, other MDS prognostic scoring systems were developed to provide survival information during the entire course of the disease. The WHO classification-based Prognostic Scoring system (WPSS) 2007 included information as the WHO classification scheme, karyotypes as described in the original IPSS categories and transfusion dependence [32]. The WPSS could be used at diagnosis or at a future time point. Some of the drawbacks of this scoring system include the lack of an absolute white blood count and platelet count, the lack of the expanded cytogenetics as was seen in IPSS-R and the absence of any criteria to support a blood transfusion [33]. This scoring system has never been validated in patients with CMML, t-MDS or MPS/myeloproliferative (MPN) syndromes.

The Global MDACC MDS Prognostic Model (MPSS, 2008) was designed to allow the evaluation of all suspected MDS patients, at any time period and included t-MDS, CMML and MDS/MPN [34]. This model improved on the prognostic accuracy of the IPSS, however the scoring system was complex and only 2 abnormal karyotypes were included. About 20% of the low risk patients with MDS as categorized by the IPSs scoring system had aggressive disease and a shortened survival. The MD Anderson Low-Risk Prognostic Scoring System (LR-IPSS+, 2008) was able to classify IPSS low and INT-1 into 3 risk groups using 5 prognostic factors [35]. This led to 3 subsets of survival for a median of 80.3 months, 26.6 months and 14.2 months. The treatment- related MDS Prognostic Scoring System (T-PSS) and the 2008, WHO subdivided patients with t-MDS into prognostic groups [36,2]. Inclusion of these patients in a prognostic scoring system was important because they had been excluded from the IPSS, IPSS-R and WPSS and some categories appear to be inherently less responsive and have a shorter survival than untreated MDS [37].

Since about 50% of the MDS patients will not have an identifiable chromosomal abnormality detected by conventional techniques, Next-Generation Sequencing (NGS) has identified recurrent genetic mutations in up to 90% of MDS patients and will be the next leap in the identification and the risk prognostication of the MDS [38]. The most common genetic mutations are found in pathways that affect Pre-mRNA splicing (SF3B1, U2AF1, SRSF2), tumor suppressors (TP 53, MYBL2, BLU), epigenetic regulators (TET2, ASXL1, DNMT3A, EZH2), impaired differentiation (RUNX1 SETBP1, ETV6) and proliferation (JAK2, NRAS, CDKN2A, PTEN) [39]. Point mutations in EZH2, ETV6, ASXL1, RUNX1 and NRAS are associated with a poor survival and somatic mutations in TP 53 and DNMT3A have a very poor prognosis, especially with an allogeneic transplantation, however SF3B1 mutations are associated with a better outcome. (Increased number of mutations in a given individual with MDS is associated with shortened survival and an increased risk of developing AML [40]. As stated, SF3B1 gene mutations have been seen in MDS with ringed sideroblasts, but has also been associated with thrombocytosis and with JAK2, CALR and MpL exon 10 mutations [41,42]. TP53 gene mutations have been identified in about 20% del (5q), have an increased risk of transformation to AML, is associated with a poor response to Lenalidomide and with a poor post allogeneic transplant outcome [43]. TET2 gene mutations are associated with an improved response to treatment with 5-Azacytidine but a poor post allogeneic transplant outcome [44]. Spliceosomal mutations in SRSF2, SF3B1 and U2AF1 are associated with a poor prognosis in chronic myelomonocytic leukemia [45].

Most patients with MDS will not die of AML, but complications of their cytopenias or age related conditions that are common in

the geriatric population such as cardiovascular disease [46]. Risk stratification will become even more accurate in the future with molecular genetic data. Haferlach, et al. developed a risk stratification model based on the mutational status of 14 genes in 944 patients with MDS combined with variables found in the IPSS that has the potential to prognosticate independently of the IPSS score [47]. Another by Bejar used another model of clinical and genetic predictors to determine prognosis in MDS [48].

The diagnosis of MDS can be difficult for a number of reasons including, the degree of dysplasia may be minimal or even undetectable, certain myeloid and lymphoid disorders can either mimic or co-occur with MDS, over 80% of early MDS patients lack a specific chromosomal abnormality and therefore have no evidence of clonality, have a mild cytopenia without dysplasia or a cytogenetic abnormality or a typical karyotype, but only mild or no dysplasia [49,50]. Molecular genetic panels have been developed that reflect the most common somatic mutations seen in MDS and to further clarify the diagnosis of MDS [49]. In the recent past, more academic and commercial labs are offering gene mutation testing from patients with cytopenias. The critical disease genes known to occur in MDS are grouped by their functional type and can aid in establishing the clonal nature of MDS. An abnormal gene mutation in a driver mutation can suggest MDS when cytopenia(s) are present, but the classic criteria for MDS in not present, such as >10% dysplasia in one or more cell lineages, 5-19% blasts in the bone marrow, an abnormal karyotype typical for MDS or evidence of clonality.

Patients who fail to meet the criteria of MDS are preliminarily classified as Idiopathic Cytopenias of Undetermined Significance (ICUS) [50]. This describes an entity in which MDS is suspected, but not proven. This provisional category requires a significant cytopenia in one or more of the hematopoietic cell lines: Hgb < 11.0 g/dL, ANC < 1,000/uL or Platelets < 100 x 10^9 and none of the classical findings of MDS such as >10% dysplasia in any cell line, myeloblasts are ≥5% of the marrow cellularity nor is there an acquired chromosomal abnormality that is specific for MDS or AML. The findings must be present for at least 6 months, the cytopenia can- not be explained by any other reason and the bone marrow does not meet the criteria for MDS. Unlike monoclonal gammopathy of undetermined significance or monoclonal B-cell lymphocytosis, clonality is not required. Some patients with ICUS will progress to MDS and progression to a myeloproliferative disorder has also been described. There exists a subset of patients with ICUS who do not demonstrate clonality, but do not fulfill the criteria for MDS. The proposed criteria for Clonal Cytopenia of Undetermined Significance (CCUS) as described by Kwok, et al. includes the same criteria for the blood and bone marrow for ICUS, however there is one or more of the following genetic findings which include as acquired chromosomal abnormality that is not diagnostic of MDS or AML and one or more of the following: an acquired chromosomal abnormality not diagnostic of a heme malignancy and the presence of a somatic mutation with a VAF ≥2% in a heme malignancy- associated gene in the peripheral blood or bone marrow [51]. They examined 144 patients that were sent to Genoptix Medical Laboratory with a diagnosis of unexplained cytopenias. The subjects were classified into MDS, ICUS with mild dysplasia and ICUS with no dysplasia and also used a 22 myeloid gene panel consisting of common genes found in myeloid malignancies. Based on conventional hematopathology, 17% were diagnosed with MDS, 15% with ICUS with some evidence of dysplasia and 69% with ICUS with no evidence of dysplasia. The bone marrow DNA was sequenced for the 22 frequently mutated genes and identified 71% of the MDS patients, 62% if the ICUS patients with some dysplasia and 20% of the ICUS patients with no dysplasia. 35% of the ICUS patients demonstrated a somatic mutation or a chromosomal abnormality and were classified as CCUS. The most common somatic mutations in MDS and ICUS were SF3B1 and TET2 mutations. The findings were confirmed in a cohort of 91 lower-risk MDS and 249 ICUS cases. Somatic mutations were found in 79% if the MDS patients, 45% of the ICUS patients with dysplasia and 17% of the ICUS patients without dysplasia. ICUS was more than five times more common than MDS and CCUS was more common than MDS.

Unfortunately, there is no specific somatic mutation that will differentiate MDS from CHIP or CCUS except SF3B1 mutations which are associated with ringed sideroblasts. Cargo, et al. attempted to distinguish characteristics that would identify those patients with early MDS from healthy individuals [52]. They identified 69 individuals who had a diagnosis of ICUS and subsequently developed MDS or AML. They performed targeted sequencing and array-based cytogenetics and were able to identify a driver mutation and/or a structural variant in 91% of the ICUS patients who progressed to MDS or AML. They state that the lack of a control group limits the diagnostic utility of their findings.

Since about 90% of MDS patients carry ≥1 oncogenic mutations and two-thirds of them are found in individuals with a normal karyotype, it would be useful if the gene mutation was specific to a category of MDS or MDS "like" disease, however it has been shown that about 10% of patients 70-79 years of age and 20% of persons 80 years or older have clonal somatic mutations detectable at a variant allele frequency (VAF) of ≥2% [53,54]. This entity has been preliminarily classified as Clonal Hematopoiesis of Indeterminate Potential (CHIP) [55]. Like monoclonal gammopathy of undetermined significance and monoclonal B-cell lymphocytosis, the transformation rate of CHIP to a hematological malignancy is about 0.5-1% a year. Although CHIP is associated with increased all-cause mortality, this entity is not MDS with certainty. Some somatic mutations have been identified in patients without cytopenias. Some of the frequently mutated genes in CHIP such as SF3B1, TP53, DNMT3A, TET2, SRSF2 and ASXL1 are also seen in myeloproliferative disorders and in acute myeloid leukemia. Even the high risk mutated genes associated with a poor prognosis such as ASXL2, RUNX1, DNMT3A and TP53 are seen with equal frequency in MDS, ICUS and CCUS.

Risk stratification will become more accurate in the future with the incorporation of next-generation sequencing. It is clear, that the only way to update the current classification of the MDS is to incorporate molecular mutations into prognostic models. This will allow for better predictive models to emerge for therapeutic decisions.

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Ann Hematol Oncol - Volume 3 Issue 3 - 2016
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Sandler S. Current and Proposed Classification Criterion and Prognostic Models for the Myelodysplastic Syndromes and Dysplastic Cytopenias of Undetermined Significance. Ann Hematol Oncol. 2016; 3(3): 1084.