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Clinical and prognostic characterization of myelodysplastic syndromes

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The myelodysplastic syndromes (MDS) provide a clinical model for evaluating the evolution of a relatively indolent malignancy into one which is frankly aggressive. The morbidity and mortality in this myeloid clonal hemopathy relate to either marrow dysfunction associated with ineffective hematopoiesis and its peripheral blood cytopenias or to disease evolution into a variant of acute myeloid leukemia (AML-MDS). MDS may arise de novo or is therapy-related (secondary, t-MDS) following treatment with chemotherapy or chemoradiotherapy for other illnesses. The disease is generally relatively indolent, with a rate of progression related to a number of defined clinical features.[1]

Morphologic classifications

The morphologic findings in MDS consist of variable degrees of dysplasia and generally increased or normal marrow hemopoietic cellularity associated with peripheral blood cytopenias and cytopathies. There are currently two morphological classification systems used to categorize MDS patients: the initial French–American–British (FAB) and the more recently proposed World Health Organization (WHO) classification.

French–American–British

The FAB group provided a marrow-based morphologic method for systematically characterizing MDS patients. These features include assessment of the proportion of myeloblasts and degree of dysplasia in the hemopoietic cells, within at least two of the three hemopoietic cell lines.[2] The characteristic

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MDS features include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes.

The FAB morphologic classification method separates patients into five subgroups: (1) refractory anemia (RA); (2) refractory anemia with ringed sideroblasts (RARS); (3) refractory anemia with excess blasts (RAEB); (4) refractory anemia with excess blasts in transformation (RAEB-T); and (5) chronic myelomonocytic leukemia (CMML). The first four entities are characterized by abnormal marrow myeloid cell differentiation patterns with RA or RARS patients having less than 5% blasts, associated with dysplasia, RAEB having between 5 and 20% blasts and RAEB-T having 20–30% blasts. RARS patients have $\geq$ 15% ringed sideroblasts. In contrast, AML is considered to be present if marrows have $>$ 30% blasts. However, to diagnose MDS more accurately, it is important to assess the relative stability (or lack thereof for at least several months) of blood counts, in addition to enumerating the marrow blast percentage and degree of dysplasia, as the patients may have an evolving form of AML. The criteria for CMML include a peripheral monocytosis exceeding 1000/mm^3, increased numbers of monocytic cells in the bone marrow, dysplasia in the erythroid, megakaryocytic or granulocytic series, and 1–20% marrow blasts.

For a generation, this classification system was quite useful clinically, particularly permitting consistent diagnostic approaches to be applied worldwide for these patients. However, difficulties emerged with the somewhat limited ability of this method to provide precise prognostic information regarding clinical outcomes in a substantial portion of patients. This limitation related to the relatively wide proportion of marrow blasts in RAEB and CMML subgroups (i.e., 5–20% and 1–20% blasts, respectively) and sole reliance of the system on marrow morphology (blast percentage) for its classification. Subsequently CMML has been usefully separated into two subgroups – proliferative and non-proliferative. The proliferative form of CMML (i.e., with leukocyte counts $>$ 12 000/mm^3, hepatosplenomegaly, constitutional symptoms) is more akin to a myeloproliferative disorder (MPD) than to MDS.[3,4] This form of CMML differs in its major clinical features from the non-proliferative (dysplastic) subtype of the disorder, which has monocytosis but relatively low leukocyte counts. These patients were previously considered to have RAEB or RA subtypes of MDS with monocytosis.

Table 1.1 Classification of myelodysplastic syndrome (MDS)

French–American–British (FAB)[2]	World Health Organization (WHO)[5–7]
NC[a]	RA (unilineage)[b]
NC[a]	RARS (unilineage)[b,c]
RA	5q− syndrome[d]
RA	RCMD
RARS	RCMD (w/RS)
RAEB	RAEB-1
RAEB	RAEB-2
RAEB-T	AML
CMML	MDS/MPD[e]
NC[a]	MDS unclassified

[a] NC, category not considered to be MDS by FAB.
[b] Requires 6 months, persisting anemia without other cause to establish the diagnosis.
[c] Pure sideroblastic anemia/idiopathic sideroblastic ineffective erythropoiesis.
[d] < 5% marrow blasts, micromegakaryocytes, and thrombocytosis; included in RA within FAB.
[e] MDS if white blood cells (WBC) $\leq 12\,000/mm^3$ (in relevant FAB category)/MPD if WBC $> 12\,000/mm^3$.

RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RAEB in transformation; CMML, chronic myelomonocytic leukemia; RCMD, RA with multilineage dysplasia; AML, acute myeloid leukemia; MDS/MPD, MDS/myeloproliferative disease.

Thus, CMML in this classification is a disorder which encompassed features of both chronic MPD and MDS.

World Health Organization

A group of hematopathologists convened by WHO recently proposed a new classification for MDS,[5–7] modifying the FAB definitions of MDS (Table 1.1). Although most prior data required at least two-line dysplasia to diagnose MDS, the WHO guidelines accept unilineage dysplasia for the diagnosis of refractory anemia and refractory anemia with ringed sideroblasts, so long as other causes of the dysplasia are absent and the dysplasia persists for at least 6 months. The latter caveat relates to the fact that a number of toxins (e.g., arsenic, alcohol) and viral infections (e.g., human immunodeficiency

virus (HIV) infection) may cause morphologic changes similar to MDS in marrow cells.[8,9]

Other categories within the WHO proposal include: (1) refractory cytopenia with multilineage dysplasia (RCMD); (2) separation of RAEB patients into those with < 10% blasts (RAEB-1) or ≥ 10% marrow blasts (RAEB-2); (3) 5q minus (5q−) syndrome; and (4) MDS unclassified. The category MDS/MPD was proposed for patients who had previously been classified as CMML.

The WHO proposals included the 5q− syndrome as a separate entity, so long as the classical features of the syndrome were met. This category requires 5q− as the sole chromosomal abnormality, RA morphologic subtype, and characteristic morphologic features, i.e., macrocytic anemia, normal or high platelet counts, hypolobulated micromegakaryocytes. The patients generally had a relatively indolent clinical course, in which evolution to AML was uncommon.[10,11] Superimposed cytogenetic lesions in addition to 5q−, however, were associated with a poorer prognosis and more progressive course.[12]

The WHO panel also suggested excluding RAEB-T patients from being considered as MDS. They proposed that patients with ≥ 20% marrow blasts should now be included as AML, rather than using the previous > 30% blast cutpoint which had been recommended by the FAB group. However, the diagnosis of MDS is not only related to blast quantitation, as these patients possess a more indolent pace of disease related to distinctive biologic features which differ from those of de novo AML.[13,14] In addition, therapeutic responses generally differ for patients in these two patient groups. AML evolving from MDS (AML-MDS) and high-risk MDS (RAEB-T) are often more resistant to standard cytotoxic chemotherapy than is de novo AML. Investigational therapy is preferable for the former patient groups.

The decision to classify and then manage patients having marrow blasts in the range of 20–30% as either AML or high-risk MDS is thus complex and needs consideration of other clinical features such as age, antecedent factors, cytogenetics, comorbidities, pace of disease, and performance status.[14] Although the WHO classification is quite useful, studies have provided conflicting evidence regarding the distinguishing features of certain subgroups in these proposals.[15,16]

Several national panels of MDS investigators and clinicians (US, Italian, and British) have provided management guidelines for the disease.[17–19] While

awaiting further data needed to clarify WHO proposals, the US National Comprehensive Cancer Network (NCCN) panel for MDS Practice Guidelines has recommended reporting both the FAB and the WHO morphologic descriptions of MDS marrow.[17] This approach permits flexibility for patient management and their entry into relevant therapeutic clinical protocols. Given the longstanding experience with FAB categorization, the British MDS Guidelines Committee recommended use of the FAB morphologic criteria, whereas the Italian Guidelines Group suggested following the WHO recommendations.[18,19]

Clinical variants

Hypocellular MDS

Although most patients with MDS have hypercellular or normocellular bone marrows, a small subgroup of MDS patients (< 15%) have marrow hypoplasia at the time of diagnosis.[20–22] Differentiation of these patients from those with either aplastic anemia or hypoplastic AML may be difficult. Most hypocellular MDS cases fit into the categories of RA and RAEB. A potentially useful means of identifying hypocellular MDS, in distinction to aplastic anemia, is the finding of an associated clonal cytogenetic abnormality.[22] In a series of patients with aplastic anemia, clonal chromosomal abnormalities were present in only 4% of individuals, and were those also seen in MDS or AML.[23]

MDS with fibrosis

Mild to moderate myelofibrosis occurs in up to 50% of all MDS subtypes, with marked fibrosis occurring in < 15% of cases, a higher proportion having these features in therapy-related MDS (t-MDS).[24] Myelofibrotic MDS is characterized by the abrupt onset of pancytopenia without organomegaly, but with substantial red blood cell anisopoikilocytosis, trilineage dysplasia, atypical megakaryocyte proliferation with hypolobated forms, and increased numbers of marrow blasts.[24,25] Occasionally a leukoerythroblastic peripheral blood picture is evident. The clinical course is generally progressive.

Secondary MDS

Secondary (i.e., therapy-related and toxic chemical-related) MDS (t-MDS) causes morbidity and mortality with or without progression to AML.[26–28] The increasing incidence of t-MDS and t-AML reflects a number of factors:

the increased longevity of many patients following more successful treatment of certain solid tumors, more intensive treatment regimens combining high-dose chemotherapy and irradiation, broader utilization of adjuvant chemo-irradiation in solid tumor therapy, environmental pollution and increased exposure to chemicals and carcinogens (particularly organic solvents).[26–28] Generally these patients have poorer prognoses than those with primary MDS. The major organic solvent implicated in leukemogenesis is benzene, with disease occurrence related to the intensity and duration of exposure to this chemical. Recent studies have indicated that polymorphisms in enzymes which detoxify benzene (e.g., NQO1), with concomitant increases in toxic metabolites capable of damaging DNA, are associated with enhanced vulnerability to benzene poisoning and development of leukemia.[26]

In t-MDS, abnormal karyotypes are evident in virtually all patients, generally with multiple chromosome aberrations, most frequently involving chromosomes 5 and 7 (85%).[29–31] The classical therapy-related MDS/leukemia involving chromosome 5 and 7 abnormalities, related to alkylating agents and irradiation, is the most common form.[27] Two additional forms of t-AML have been described: one type attributed to exposure to topoisomerase II-active chemotherapeutic agents (e.g., etoposide) and involving the chromosome 11q23 locus, and the other involving the chromosome 21q22 locus.[29,32] The benzene-induced cytogenetic abnormality is frequently trisomy 9.[33]

Prognostic determinations

Morphologic assessment: FAB

Mortality in MDS relates to the patient's morphologic subtype and is due to a variety of causes, including evolution to AML, infection, or bleeding complications associated with the patient's dominant cytopenia(s). Since most MDS patients are elderly, concomitant non-hematologic diseases also substantially contribute to their morbidity and mortality. Utilizing FAB subgroup morphologic criteria, there was a moderate degree of precision regarding prognostic findings for survival and AML evolution (Table 1.2, Fig. 1.1).[34–38] Patients with RAEB and RAEB-T had relatively poor prognoses, with median survivals generally ranging from 5 to 12 months, in contrast to RA or RARS patients with median survivals of 3–6 years. The proportion of these individuals who transformed to AML varied similarly: in the higher-risk RAEB

Table 1.2 Myelodysplastic syndrome: survival and leukemic evolution related to FAB morphologic subgroups[a]

	FAB subgroups				
	RA	RARS	RAEB	RAEB-T	CMML
Median survival (months)	43	73	12	5	20
Transformation to AML (percent)	15	5	40	50	35
Proportion of patients (percent)	25	15	35	15	10

[a] Meta-analysis.

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FAB, French–American–British; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RAEB in transformation; CMML, chronic myelomonocytic leukemia; AML, acute myeloid leukemia.

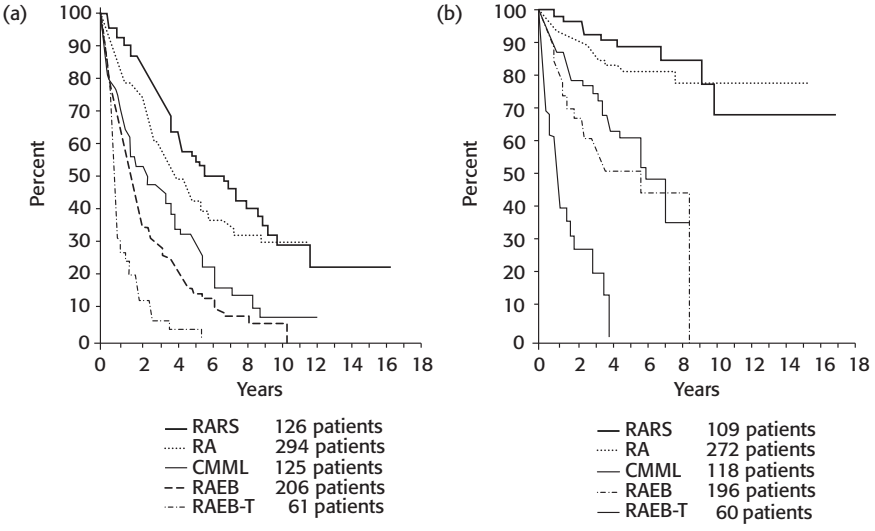

Fig. 1.1 (a) Survival and (b) freedom from acute myeloid leukemia evolution in patients with myelodysplastic syndrome who were evaluated by the International MDS Workshop, in relation to their French–American–British classification subgroup (Kaplan–Meier curves). RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RAEB in transformation; CMML, chronic myelomonocytic leukemia. This research was originally published in Blood[46]. Greenberg, P., Cox, C., Le Beau, M. M. *et al.* International Scoring System (IPSS) for evaluating prognosis in myelodysplastic syndrome. *Blood*, 1997; **89**, 2079–88. © the American Society of Hematology.

and RAEB-T patients this incidence was 40–50%, whereas in the remainder of the patients it was 5–15%. Regarding time to disease evolution, 25 and 55% of patients with RAEB and RAEB-T, respectively, underwent transformation to AML at 1 year, and 35 and 65% at 2 years. In contrast, for patients with RA this incidence was 5 and 10% at 1 and 2 years, whereas none of the RARS patients underwent leukemic transformation within 2 years. Patients with higher marrow blast percentages had poorer prognoses, with specific cutpoints of > or < 10% marrow blasts having major impact on survival.[34]

For CMML patients, the major prognostic feature for their survival (as for the other MDS subgroups) was their marrow blast percentage.[39–42] Median survival of CMML patients with < 5% marrow blasts was 53 months, versus 16 months (similar to RAEB) for those with 5–20% blasts. Monocytosis greater than 2600/mm^3 and abnormal cytogenetics also correlated with poor survival. The separation of these patients into proliferative and nonproliferative/dysplastic subgroups (based on their leukocyte counts) is supported by evaluation of their clinical outcomes.[3,41] CMML patients have also been further subdivided into four prognostic risk groups based on a combination of independent predictive factors: (1) level of marrow blasts; (2) degree of anemia; (3) peripheral blood immature mononuclear cells; and (4) lymphocytes.[43] In CMML and other MDS patients, the presence of a number of gene mutations (e.g., *ras, fms, flt3*), high lactate dehydrogenase, and high beta$_2$-microglobulin levels were also associated with poorer prognoses (see below).[44,45]

Other suggested independent morphologic prognostic indicators are the presence of myelofibosis or of Auer rods. MDS patients with myelofibrosis generally have poorer survivals than those without fibrosis.[24] In the FAB classification, the presence of Auer rods in myeloid cells implied the diagnosis of RAEB-T. However, the adverse prognostic influence of Auer rods per se has not been clearly demonstrated.

Morphologic assessment: WHO

The WHO classification has helped to morphologically stratify the prior heterogeneous histologic subtypes of some FAB-categorized MDS patients. Prognostic data have been obtained with this categorization, although the degree of inconsistency in reported clinical outcomes warrants further evaluation.[14–16] Those patients with uni- versus multilineage dysplasia

(refractory cytopenia with multilineage dysplasia – RCMD) have differing prognoses, with RCMD generally having poorer clinical outcomes.[15] Clear previous evidence has demonstrated the importance of separating RAEB patients into those with < or > 10% marrow blasts,[34,46] thus the RAEB-1 and -2 WHO categories appear clinically useful.

The classical 5q− syndrome has a generally low risk of transformation to acute leukemia, and favorable prognosis.[11,47] The better survival of 5q− syndrome patients compared to other MDS patients is also associated with a low incidence of deaths from infection and bleeding. Non-hematologic illnesses and hemosiderosis from red blood cell transfusion dependence constitute major causes of morbidity and mortality in this group of patients. The presence of karyotypic abnormalities in addition to 5q− or > 5% marrow blasts is associated with a worse prognosis.[12] Of interest is the distinctive responsiveness of this subgroup of MDS patients to a recently evaluated biologic agent, Revlimid (CC5013).[48]

Atypical localization of immature precursors

Studies analyzing marrow biopsies have demonstrated that some MDS patients had clusters of blast cells in central marrow regions, rather than being normally paratrabecular, referred to as abnormal localization of immature myeloid precursors (ALIP). Patients with these morphologic findings had significantly shorter survival in all subtypes of MDS.[49,50] ALIP-positive cases were more common in RAEB, RAEB-T, and CMML.

Biologic assessment

In vitro hemopoietic clonogenic assays

Despite the more indolent nature of MDS than AML, many in vitro hemopoietic clonogenic abnormalities evident in AML are also present in MDS. These biological parameters have been useful for evaluating pathogenetic mechanisms and prognosis in MDS patients.[51] The colony-forming capacities of all of the marrow hemopoietic precursor cells (CFU-GEMM, BFU-E, CFU-E, CFU-GM, CFU-Meg) are quite low or absent in the majority of MDS patients, as found in most AML patients. Also similar to leukemic patients, an increased proportion of CFU-GMs are of light buoyant density, have abortive myeloid cluster formation, and defective cellular maturation occurs within the colonies.

Table 1.3 Prognosis of myelodysplastic syndromes: utility of in vitro marrow myeloid clonogenic culture studies

Growth patterns	Incidence (%)	Transformation AML (%)	Median survival (months)
RAEB-T ($n = 80$)[52,53]		51 (45–60)	9 (7–11)
Non-leukemic growth	33 (27–38)	31 (29–33)	20 (15–25)
Leukemic growth	68 (62–73)	60 (50–70)	7 (5–8)
RAEB ($n = 17$)[54,55]		41	14
Non-leukemic growth	70	29	21
Leukemic growth	30	100	10
RA ($n = 82$)[53,56,57]		39 (35–44)	24 (9–20)
Non-leukemic growth	54 (30–74)	20 (21–40)	47 (9–50)
Leukemic growth	46 (26–70)	60 (50–80)	8 (4–10)

Mean values and ranges of means for cited studies.

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AML, acute myeloid leukemia; RAEB-T, refractory anemia with excess blasts in transformation; RA, refractory anemia.

In vitro marrow myeloid (CFU-GM) clonal growth in MDS may be divided into leukemic and non-leukemic patterns.[51] Leukemic-type growth includes micro- or macrocluster formation with defective maturation or blasts within the aggregates, single persisting blasts, or very low colony formation (< 2 colonies per 10^5 marrow cells). Non-leukemic growth is marked by having persisting colony formation, even if moderately decreased in frequency. As shown in Table 1.3, six studies involving 179 MDS patients with differing FAB morphologic subtypes demonstrated correlation between clinical outcome and in vitro marrow growth.[51–57] When patients were stratified according to their in vitro myeloid growth patterns, subgroups of MDS patients with non-leukemic growth patterns had a 20–31% incidence of transformation to AML and 20–47-month median survivals. In contrast, MDS patients with leukemic growth patterns had a 60–100% incidence of transformation and 7–10-month median survivals. MDS patients with single hemopoietic cell line defects, such as idiopathic sideroblastic ineffective erythropoiesis and idiopathic neutropenia with a low propensity to leukemic evolution,