THE DIAGNOSTIC SPECTRUM OF MDS, MDS/MPN, AND MF

*MDS Prognostic Scoring System: IPSS-R

Prognostic Variables
Cytogenetic results (category)
Bone marrow blasts (%): <=2.0; >2.0-<5.0, 5.0-10.0, >10.0
Degree of anemia (Hgb in g/dl) ≥ 10 vs. 8-10 vs. < 8
Degree of neutropenia (x 10^9/L) ≥ 0.8 vs. < 0.8
Degree of thrombocytopenia (x 10^9/L) >100 vs. 50-99 vs. <50

Other prognostic scoring systems such as WPSS include WHO risk classification, transfusion dependence, and cytogenetic class. The MDACC model incorporates age, performance status, leukocytosis, degree of anemia/ thrombocytopenia, marrow blasts, and cytogenetic class.

Greenberg, et al. Blood. 2012;120(12):2454.
Malcovati et al. J Clin Oncol. 2007;25(23):3503.
Kantarjian et al. Cancer. 2008;113(6):1351.
Arber et al. Blood. 2016; 127:2391-2405.

In a large study conducted by the IWG-MDS, mutations involving TP53, CBL, EZH2, RUNX1, U2AF1, and ASXL1 had an independent, adverse impact on prognosis.
Pts with mutated SF3B1, or without any such mutation had a more favorable prognosis.

Bejar et al. Abstract#907.
Presented at the ASH Annual Meeting, December 7, 2015; Orlando, FL.

***See www.aamds.org/mdsrisk for summary of MDS prognostic scoring systems**

Prognosis in Primary Myelofibrosis

	Lille	IPSS	DIPSS	DIPSS Plus
Anemia (Hgb < 10g/dl)	x	x	x	x
WBC > 25 x 10^9/L	x*	x	x	x
Circulating blasts ≥ 1%		x	x	x
Constitutional symptoms		x	x	x
Age > 65		x	x	x
Abnormal karyotype (-8,-7,-5, i17q,12p-,inv3, 11q23 or Complex)				x
Platelets <100 x 10^9/L				x
RBC transfusion dependence				x
	Dupriez 1996	Cervantes 2009	Passamonti 2010	Gangat 2011

*The Lille score identified a WBC > 30 x 10^9 or a WBC of < 4 x 10^9 as adverse indicators

(IPSS) Cervantes et al. Blood. 2009; 113: 2985-2901.
(DIPSS)Passamonti et al. Blood. 2010; 115: 1703-1708.
(DIPSS-plus) Gangat et al. J Clin Oncol. 2011;29(4):392.
Dupriez et al. Blood. 1996; 88:1013–1018.
Please look at each individual paper for the exact score calculation.

*The impact of the driver mutational profile on prognosis is becoming more clear. Pts with *CALR* mutations have a more favorable outcome, compared to those with *JAK2* or *MPL* mutations, and especially those that lack *JAK2/CALR/MPL* ("triple-negative").

Mutations in other genes also impact prognosis, and those with 1 or more mutations involving *ASXL1, IDH, EZH2,* and *SRSF2* have a high risk profile. A particularly high risk profile may include pts that are *CALR wild-type/ASXL1* mutated.

Rumi et al. Blood 2014; 124:1062-1069;
Vannucchi et al. Leukemia 2013; 27(9):1861-1869;
Guglielmelli et al. Leukemia. 2014; 28(9):1804-1810;
Tefferi et al. Leukemia. 2014; 28(7): 1472-1477.

MDS/MPN Prognostic Variables

Prognostic Variables in CMML
Advanced age (> 65)
Decreased hemoglobin (< 10 g/dl)
*Red cell transfusion dependency
Decreased platelets (< 100 x 10^9/L)
Increased absolute monocyte count (> 10 x 10^9/L)
Circulating immature myeloid cells
CMML FAB subtype (*leukocyte < 13 x 10^9/L more favorable)
CMML WHO subtype (worse prognosis w/ increasing PB/*BM blasts)
*Cytogenetic risk category Low: Normal or –Y High: +8, abn of 7, complex Intermediate: All others
*Presence of *RUNX1, NRAS, SETBP1, ASXL1* mutations

*CPSS-Mol: Elena, C et al. Blood. 2016; 128(10): 1408-1417.
Mayo Model: Patnaik et al. Leukemia. 2013; 27(7):1504-1510.
CPSS: Such et al. Blood. 2013; 121:3005-3015.
Itzykson et al. J Clin Oncol. 2013; 31 (19):2428-2436.

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THE DIAGNOSTIC SPECTRUM OF MDS, MDS/MPN, AND MF

MDS: Refractory Cytopenias and Dysplasia

Clinical features

- Constitutional symptoms less likely
- Refractory cytopenia(s)
- Organomegaly unusual

Blood and marrow findings

- Hyper > hypocellularity
- ↑Peripheral/marrow blasts
- Single or multi-lineage dysplasia
- +/-ring sideroblasts

Cytogenetic and molecular features

- CKA in 40-70%, even in absence of dysplasia (commonly 5q-, -7 or 7q-, +8, 20q-, and –Y)

Mutations in *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53*, and *EZH2* are commonly identified, but their presence alone is insufficient to make a diagnosis of MDS

MDS/MPN Overlap Syndromes: Dysplastic Cytopenias with Proliferation

Clinical features

- +/- Constitutional symptoms
- Cytopenia(s) with cytosis:
  - Thrombocytosis (MDS/MPN with ring sideroblasts and thrombocytosis)
  - Monocytosis (CMML)
  - Neutrophilia (a CML)
- Organomegaly

Blood and marrow findings

- Marrow hypercellularity
- ↑Peripheral/marrow blasts
- Dysplasia
- Ring sideroblasts (RARS-T)

Cytogenetic and molecular features

- CKA in ~30% of CMML (+8, del(5q), +10, -11q, -12p, +17p, +19, and +21, and –Y)
- *JAK2* V617F mutation (~50%) in MDS/MPN with ring sideroblasts and thrombocytosis often co-mutated with *SF3B1* mutations

CSF3R mutations are rarely identified in aCML, whereas *SETBP1* and/or *ETNK1* mutations can be seen in up to 30% of aCML cases

SRSF2, TET2, and/or *ASXL1* are frequently identified in CMML, whereas *SETBP1, NRAS/KRAS, RUNX1, CBL*, and *EZH2* are less frequently identified

Myelofibrosis: Myeloproliferation

Clinical features

- Constitutional symptoms likely
- Cytopenia or cytosis
- Increased LDH
- Organomegaly

Blood and marrow findings

- Leukoerythroblastosis
- ↑Peripheral/marrow blasts
- Variable cellularity
- Proliferating/atypical megakaryocytes
- Reticulin/collagen fibrosis

Cytogenetic and molecular features

- CKA in ~50% (20q- ,13q- , abn chromosome 1 or 12, +8,+9, -5, and -7)
- *JAK2* V617F *(60%);*
- *CALR (20-25%);*
- *MPL (<10%)*

CKA: clonal karyotypic abnormality
CMML: chronic myelomonocytic leukemia
aCML: atypical CML

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