Lower-Risk MDS

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Case presentation

81M w CKD (b/l Cr 1.8), HFpEF (admitted 2x last year), AF (on apixaban), p/w hgb 10.1, MCV 99.

Feels fine overall, some DoE that is longstanding, doing well since last admission and diuresis.

No frequent infections.

Doesn't have dentures, no OTC supps.

Case presentation

Labs

- hgb 10.1, MCV 99
- plt 132
- WBC 5.3, normal diff
- folate, B12 replete
- TSAT 19%

Case presentation

Given 1g IV iron, seen back in 10wks, BMBx scheduled prophylactically

hgb 9.6, MCV 97

other counts unchanged

Case presentation

BMBx

- 35% cellularity
- blasts 1%
- dysplasia in 15% of erythroid precursors (megaloblastic erythroblasts, basophilic stippling, cytoplasmic vacuolation)
- no ringed sideroblasts
- del(5q)
- NGS pending

Questions

How common is MDS?

What do people present with?

How do we risk-stratify MDS?

What are the relative incidences of the risk strata?

When do we intervene in lower-risk disease?

What tools do we have?

How do we sequence therapies?

Can we impact prognosis?

Epidemiology

yearly incidence: 4/100,000[1]

incidence increases with age:[2]

- <40yo: 0.1/100,000
- >65yo: 25/100,000
- 70-79yo: 30/100,000
- >80yo: 60/100,000
- underreported: yearly incidence >65yo may be as high as 75/100,000[3]

median age of dx: 70-75

male predominance

- 5.4/100,000 vs 2.9/100,000 in women

S/sx prevalence (%)[1]

Fatigue	55
Hgb <10 g/dL	52
Plt <100 x 10^9/L	40
ANC <800 x 10^9/L	18
Fever/infection	15
Bleeding	8

[1] Sekeres

Diagnosis

≥1 cytopenias
  hgb <10, ANC <1800, plt <100k

≥10% dysplastic cells in ≥1 lineage*

<20% blasts

presence of certain cytogenetic/molecular findings
  absence of AML-defining (cyto)genetics (e.g. t(8;21), CBFB-MYH11)

* if certain cytogenetic changes**, can dx MDS w/o dysplasia (<10% of cases)

** monosomy 5, 7, or 13; 5q, 7q, and 13q deletions; i(17p) and t(17p); 11q deletion; 9q or 12p deletion; or t(12p), idic (X)(q13)

Risk stratification

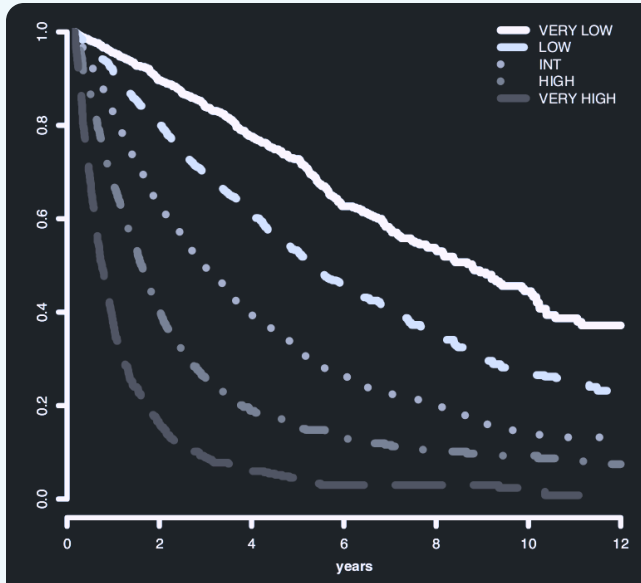

Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

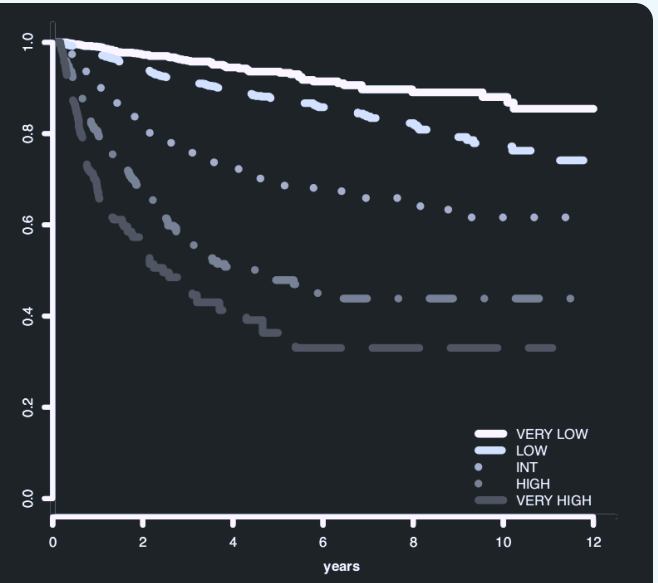

Figure 4. AML evolution based on IPSS-R prognostic risk-based categories. Progression to AML related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 6485; Dxy 0.52, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Risk stratification (IPSS)

Variable	Score				
	0	0.5	1	1.5	2
Bone marrow blasts (percent)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor	-	-
Cytopenias	0-1	2-3	-	-	-

Karyotype stratification:

Good: Normal, -Y, del(5q), del(20q)

Intermediate: not good nor poor

Poor: ≥3 abnl, chromosome 7 abnl

Risk stratification (IPSS)

Risk group	IPSS score
Low	0
Intermediate-1	0.5 to 1
Intermediate-2	1.5 to 2
High	2.5 to 3.5

Risk stratification (IPSS-R)

	0	0.5	1.0	1.5	2.0	3.0	4.0
blast %	≤2		>2 - <5		5 - 10	>10	
hgb	≥10		8 - <10	<8			
plt	≥100	50 - 100	<50				
ANC	≥0.8	<0.8					
cytogenetics	very good -Y, del(11q)		good normal, del(12p), del(20q),		intermediate single NOS, del(7q),	poor -7, double w -7/del(7q), inv(3)/t(3q)/del(3q),	very poor >3 abnl

Risk stratification (IPSS-R)

Risk group	IPSS-R score
very low	≤1.5
low	>1.5 to 3.0
intermediate	>3 to 4.5
high	>4.5 to 6
very high	>6

Risk stratification (IPSS-many)

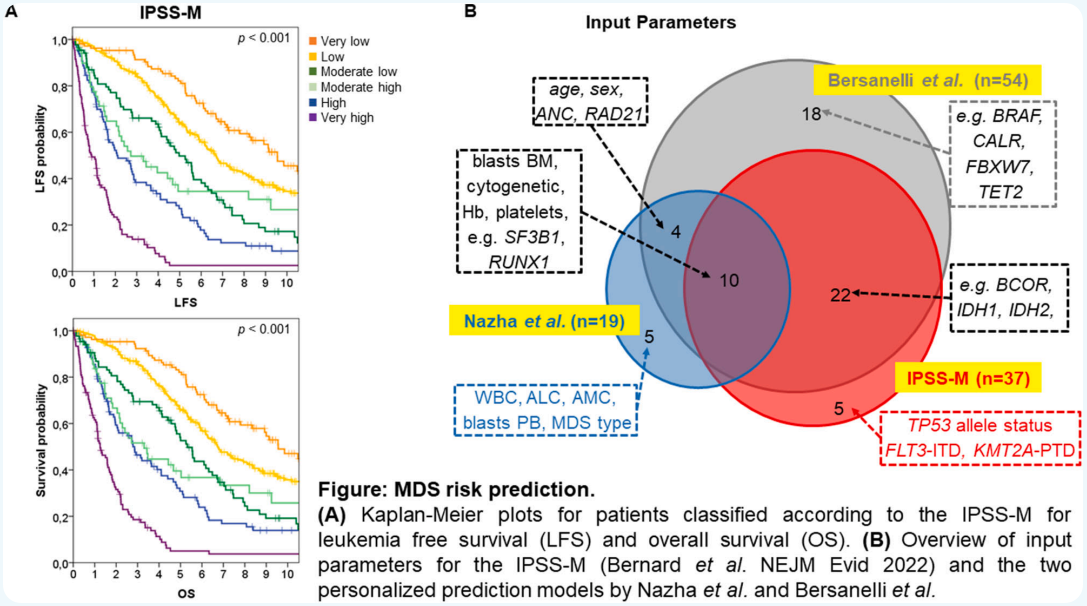

Figure: MDS risk prediction.
(A) Kaplan-Meier plots for patients classified according to the IPSS-M for leukemia free survival (LFS) and overall survival (OS). **(B)** Overview of input parameters for the IPSS-M (Bernard *et al.* NEJM Evid 2022) and the two personalized prediction models by Nazha *et al.* and Bersanelli *et al.*

Newer risk stratification strategies attempt to address shortcomings with prior models (e.g. new mutations of significance, significant heterogeneity within risk groups). Because they are complex, they are not in widespread use outside of research settings.

[1] Baer et al

Management

Goals of management

No interventions have been shown conclusively to improve OS in LR-MDS.[1]

- reduce sx
- reduce tfx dependence
- minimize morbidity
- balance tox of tx vs tox of dz

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[1] there is now a suggestion that early EPO may improve OS (Garelius 2022, abstract at the EHA Annual Congress)

Management - anemia

EPO

relatively high dose, e.g. 60,000u EPO q7d, 500 µg darbepoetin alfa q21d

meta-analysis: ~40% response rate overall (hgb up 1-1.5g, reduction in tfx)

2017 RCT: 15% RR at 24wk (0% in placebo)
Open-label 48wk f/u: 35% RR

response rate is higher if lower baseline EPO (e.g. <200 IU/L)
if high tfx dependence (≥1 tfx/14d) and EPO >200, RR <10%

mean duration of response: 8-23mo

Management - anemia

luspatercept

- TGF-b superfamily, promotes late-stage erythropoeisis
- MDS-RS (usu SF3B1-mutant)
- tfx independence in ~40% (~10% in placebo)[1]
- median duration of response ~30wks
- diarrhea, nausea, back pain, dizziness in 20%

lenalidomide

- del(5q) (sometimes non-del(5q) if used in combo w epoeitin alfa)
- 21/28d cycles

Management - anemia - new stuff

imetelstat

- telomerase inhibitor
- IV, 2h infusion q4wks
- "IMerge" trial (phase 2 complete, phase 3 finished recruiting)
- R/R tfx burden (≥4 pRBC/8wks)
- primary endpoint: transfusion independence ≥8wk
- 37% reached primary endpoint

Management - anemia - new stuff

roxadustat

- HIF inhibitor (approved in China for CKD, not approved in US d/t c/f thrombosis, CV events)
- oral, 3x/wk
- phase 3, LR-MDS, <5% blasts, low tfx burden
- ~50% reduction in tfx
- EPO level doesn't seem to matter, but sample size is small

H3B-8800

Management - thrombocytopenia

romiplostim[1]

- plt <20k: 1250 vs 1800 plt tfx per 100 pt-years
- plt >20k: 80 vs 225 bleeding events per 100 pt-years

eltrombopag[1]

- baseline plt <30k
- improved plt count in 50% (3% in placebo)

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[1] TPO possibly yield higher risk of AML transformation, particularly in MDS-EB, but longer f/u studies failed to show an association (e.g. Kantarjian 2018)

Management - multipenia/neutropenia

HMA

- may be able to use 3d cycles, rather than 5/7
- 29% CR or PR (12% w best supportive care)
- oral azacitidine
  - CC-486, "Onureg"
  - RBC-TI 31% (placebo 11%)[1]
  - this study used IPSS: ~30% would have been upstaged w IPSS-R

ATG

Management

MDS-hypoplastic

- LR-MDS w <25% cellularity appears to somewhat overlap w aplastic anemia
- so -> ATG, cyclosporine, etc.

HemOnc.org entry

NCCN Guidelines

PathologyOutline