Risk Stratification in Hypomethylating Agent-Treated Patients with Myelodysplastic Syndromes: A Multivariate Model

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INTRODUCTION

HYPOMETHYLATING AGENTS (HMA)

- Azacitidine, decitabine, and decitabine/ cedazuridine are standard of care for patients with myelodysplastic syndrome (MDS)
- Increased survival with HMAs but low durable response rates and transient benefits

MOLECULAR INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-M)

- Recently developed to risk stratify patients with the addition of mutational data to conventional cytogenetics, bone marrow blasts, and blood counts
- Shown to improve prognostication in all MDS patients at baseline in several large studies
- Applicability in specifically patients undergoing treatment with HMA remains unknown

METHODS

- **AIM:** to assess the applicability of IPSS-M to patients who received frontline HMA therapy for MDS
- Retrospective evaluation of patients diagnosed with MDS seen at MD Anderson Cancer Center between 2017-2021 (with availability of 81-gene target PCR-based NGS platform)
- Covariates compared between groups in univariate analysis
- Multivariate model established using Cox proportional hazard model with age, gender, peripheral blood counts, cytogenetics, and mutations present in at least 3 patients
- Backward feature selection was used to obtain final parsimonious multivariate model
- Models compared using Akaike Information Criterion

RESULTS

- 455 patients evaluated as new patients and initiated on frontline treatment with HMA

FIGURE 1. MOST COMMONLY-MUTATED GENES

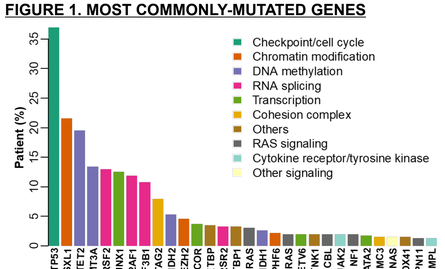


TABLE 1. PATIENT CHARACTERISTICS AT DIAGNOSIS.

	N (%)/Median [Range], n=455
Age (years)	69 [22-90]
Male	289 (64)
Therapy-related MDS	160 (35)
Laboratory Values	
BM blasts (%)	4 [0-20]
WBC (K/μL)	2.90 [0.40-34.40]
ANC (K/μL)	1.25 [0.05-25.90]
Hemoglobin (g/dL)	9.10 [5.20-16.20]
Platelets (K/μL)	59 [7-647]
Cytogenetic risk categories by IPSS-R*	
Very good	6 (1)
Good	167 (37)
Intermediate	74 (17)
Poor	55 (12)
Very poor	146 (33)
Normal karyotype*	152 (34)
Complex cytogenetics*	167 (37)
IPSS-R category*	
Very low	14 (3)
Low	78 (17)
Intermediate	97 (22)
High	113 (25)
Very high	146 (33)
IPSS-M category	
Very Low	6 (1)
Low	73 (16)
Moderate Low	51 (11)
Moderate High	54 (12)
High	108 (24)
Very High	163 (36)

*Cytogenetics not available in 7 patients

MDS: myelodysplastic syndromes; BM: bone marrow; WBC: white blood cell; ANC: absolute neutrophil count; IPSS-R: Revised International Prognostic Scoring System; IPSS-M: Molecular International Prognostic Scoring System

FIGURE 2. OVERALL SURVIVAL BY IPSS-R AND IPSS-M

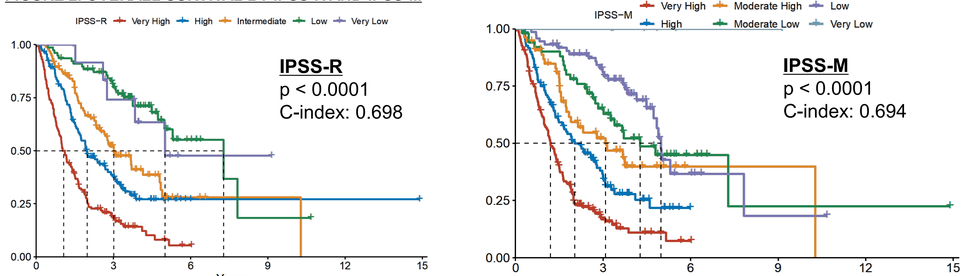


FIGURE 3. RECLASSIFICATION BY IPSS-R TO IPSS-M

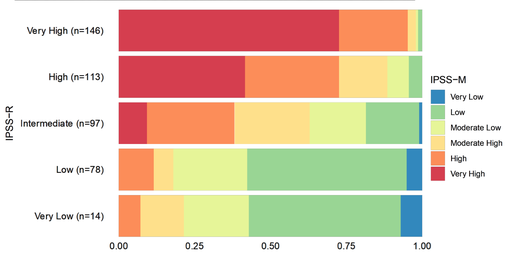


TABLE 2. MULTIVARIATE ANALYSIS MODEL FOR OVERALL SURVIVAL

Variable	Hazard Ratio (95% CI)	p-value	Model Weight
Age at diagnosis	1.02 (1.01, 1.03)	0.005	0.018
Anemia*	1.18 (1.10, 1.27)	<0.001	0.169
Thrombocytopenia**	1.02 (1.01, 1.04)	0.002	0.024
BM blasts	1.04 (1.02, 1.07)	<0.001	0.043
Cytogenetic risk score***	1.35 (1.19, 1.53)	<0.001	0.299
TP53 mutation status****	1.92 (1.39, 2.67)	<0.001	0.654
U2AF1	0.57 (0.37, 0.89)	0.014	-0.555
PTPN11	2.75 (1.18, 6.40)	0.019	1.010

*Measured by unit [g/dL] of hemoglobin decrease.
**Measured by 10 units [x10^9] of platelet decrease.
***By IPSS-R.
****Includes both monoallelic (score 1) and biallelic (score 2).

- "DOWN" – downstaging of disease from IPSS-R higher-risk to IPSS-M lower-risk MDS
- "UP" – upstaging of disease from IPSS-R lower-risk to IPSS-M higher-risk MDS

Cohort	mOS	95% CI	IPSS-R mOS	IPSS-M mOS
DOWN n=16	39.1	28.6, NE	20.0 (HR-MDS)	60.0 (LR-MDS)
UP n=17	37.1	26.8, NE	63.6 (LR-MDS)	18.7 (HR-MDS)

- No differences by IPSS-M in IPSS-R intermediate-risk patients (p = 0.290)

FIGURE 4. MEDIAN OVERALL SURVIVAL BY 6-GROUP MULTIVARIATE MODEL

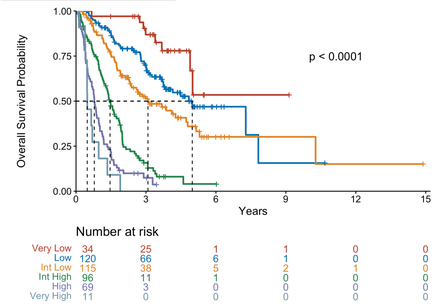


TABLE 3. SUMMARY OF CLINICAL OUTCOMES OF 6-GROUP MULTIVARIATE MODEL

	Very Low	Low	Moderate Low	Moderate High	High	Very High
Number of Patients (%)	34 (7.6)	120 (27.0)	115 (25.8)	96 (21.6)	69 (15.5)	11 (2.5)
Risk Score	≤ -0.8	> -0.8 to 0	> 0 to 0.8	> 0.8 to 1.6	> 1.6 to 2.4	> 2.4
Hazard Ratio (95% CI)	0.46 (.022, 0.97)	1.0 (reference)	1.58 (1.09, 2.30)	4.67 (3.25, 6.73)	9.11 (6.16, 13.5)	15.7 (8.0, 30.9)
Median LFS (IQR) [years]	4.999 (3.444, NE)	3.105 (2.765, 4.621)	2.319 (1.744, 2.992)	0.997 (0.890, 1.331)	0.572 (0.446, 0.783)	0.482 (0.400, NE)
Median OS (IQR) [years]	NR (4.893, NE)	4.986 (3.751, NE)	3.086 (2.355, 4.791)	1.459 (1.262, 1.859)	0.783 (0.676, 0.997)	0.482 (0.471, NE)
Transformation to AML [%]						
By 1 yr	0	7.5	5.2	15.6	29	27.3
By 2 yr	0	10.8	17.4	32.3	40.6	45.6
By 4 yr	5.9	15	19.4	35.4	40.6	45.6
Death without AML [%]						
By 1 yr	3.2	8	18.3	40.3	65.8	100
By 2 yr	6.5	25	38.7	77.4	85.4	100
By 4 yr	61	71	75.3	96.8	100	100

TABLE 4. COMPARISON OF RISK STRATIFICATION MODELS BY AKAIKE INFORMATION CRITERION

Risk Stratification Model	Number of Parameters	AICc*	Change in AICc
6-Group Multivariate	5	2823.64	0
5-Group Multivariate	4	2832.25	8.61
IPSS-R	4	2933.95	110.31
IPSS-M	5	3002.97	179.33

AICc: corrected Akaike Information Criterion; IPSS-R: Revised International Prognostic Scoring System; IPSS-M: Molecular International Prognostic Scoring System

CONCLUSIONS

- IPSS-M did not provide additional prognostic power over IPSS-R with C-indices < 0.7
- Prognostication improved over both IPSS-R and IPSS-M by novel multivariate scoring system
- Further validation of this scoring system is warranted

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