Disease Characteristics and Outcomes of Hypomethylating Agent Failure in Patients with Myelodysplastic Syndromes

Kelly S. Chien[1], Kunhwa Kim[1], Ziyi Li[2], Rashmi Kanagal Shamanna[3], Faustine Ong[1], Guillermo Montalban Bravo[1], Tapan M. Kadia[1], Elias J. Jabbour[1], Naveen Pemmaraju[1], Danielle E. Hammond[1], Nicholas J. Short[1], Farhad Ravandi[1], Yesid Alvarado[1], Sherry A. Pierce[1], Xiao Qin Dong[1], Hagop M. Kantarjian[1], Guillermo Garcia-Manero[1]

The University of Texas MD Anderson Cancer Center, [1]Department of Leukemia, [2]Department of Biostatistics, [3]Department of Hematopathology, Houston, TX, USA

INTRODUCTION

HYPOMETHYLATING AGENTS (HMA)

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

HMA FAILURE (HMA-F)

- Refers to patients who do not respond to or progress on HMA therapy
- Median overall survival after HMA failure:
  - Higher-risk MDS: 4-6 months
  - Lower-risk MDS: 13 months
- No approved treatments after HMA failure with increased risk of transformation to acute myeloid leukemia (AML)

METHODS

- Aim: to assess the clinicopathologic characteristics and outcomes of patients with HMA-F MDS
- Retrospective evaluation of patients diagnosed with MDS seen at MD Anderson Cancer Center between 2017-2021
- Data collection (at diagnosis (DX) and at HMA-F)
  - Patient characteristics/laboratory values
  - Bone marrow data (blast percentage, cytogenetics (CG), next generation sequencing (NGS) information)

RESULTS

FIGURE 1. PATIENT COHORT

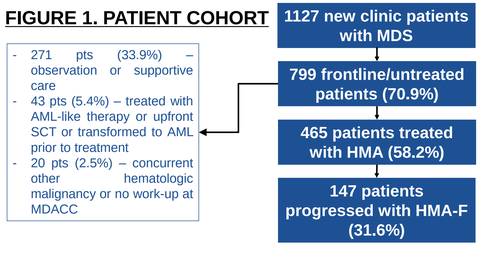


TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WHO DEVELOP HMA FAILURE

	N (%)/Median [Range], n=147
Age (years)	70 [40-90]
Male	89 (61)
Therapy-related MDS	55 (37)
Number of HMA cycles	7 [1-37]
HMA monotherapy	98 (67)
HMA combination therapy	49 (33)
IPSS-R Category*	
Very low	1 (1)
Low	12 (8)
Intermediate	30 (24)
High	42 (29)
Very high	57 (39)
Cytogenetic risk categories by IPSS-R*	
Very good	2 (1)
Good	47 (33)
Intermediate	22 (15)
Poor	16 (11)
Very poor	55 (39)
Number of mutations**	2 [0-7]
TP53	63 (44)
ASXL1	31 (21)
TET2	27 (19)

TABLE 2. LABORATORY VALUES AT TIME OF HMA FAILURE

	Median at DX [range]	Median at HMA Failure [range]	P-value*
BM blasts (%)	6 [0-18]	10 [0-91]	**<0.001**
WBC (K/μL)	2.8 [0.5-34.4]	1.9 [0.4-89.6]	0.921
ANC (K/μL)	1.3 [0.1-25.9]	0.6 [0.0-57.3]	0.633
Hgb (g/dL)	8.9 [6.2-15.0]	8.8 [5.4-15.8]	0.281
Platelets (K/μL)	63 [7-636]	38 [0-630]	**<0.001**
Cytogenetics			
Clones	2 [1-3]	1 [1-3]	0.327
Abnormalities	1 [0-24]	2 [0-23]	**<0.001**
Mutations	2 [0-8]	2 [0-11]	**<0.001**

OVERALL SURVIVAL

- mOS from HMA-F: 6.8 months (95% CI: 5.5, 9.3)
- Median time from DX to HMA-F: 10.9 months [range: 1.3-70.5]
- Median follow-up time from HMA-F: 24.0 months

FIGURE 2. OVERALL SURVIVAL FROM TIME OF HMA-F BY IPSS-R

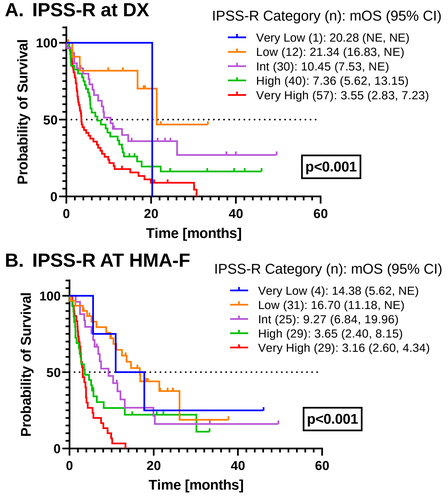
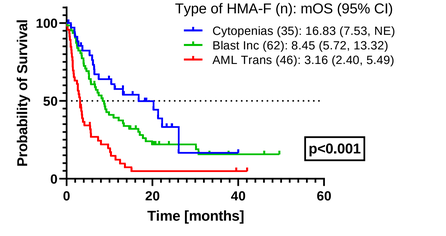


FIGURE 3. OVERALL SURVIVAL FROM TIME OF HMA-F BY TYPE OF FAILURE



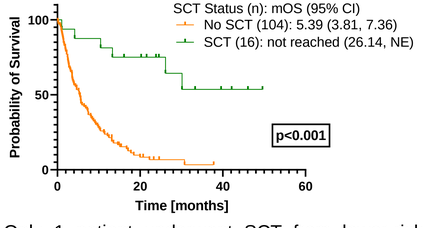
OVERALL SURVIVAL BY HMA THERAPY

- Patient groups:
  - Lower-risk MDS (IPSS-R ≤ 3.5): n=20
  - Higher-risk MDS (IPSS-R ≥ 4): n=120
- Higher-risk patients: mOS differences with HMA monotherapy vs combination therapy and number of cycles of HMA therapy (≤6 vs >6)

Therapy	Pts	OS since HMA-F	P-value
HMA alone	75	8.75 (5.65, 13.2)	**< 0.001**
ICPI*	16	7.71 (2.76, NE)	
CD47	6	2.92 (1.25, NE)	
BCL2	10	3.79 (2.83, NE)	
APR	6	2.79 (1.05, NE)	
Other**	7	8.15 (5.49, NE)	

*anti-PD-1/PD-L1/CTLA-4, anti-TIM-3
**targeted therapy, lirilumab, rigosertib

FIGURE 4. OVERALL SURVIVAL FROM TIME OF HMA-F IN HIGHER-RISK PATIENTS BY SCT



- Only 1 patient underwent SCT from lower-risk MDS cohort

TABLE 3. FACTORS ASSOCIATED WITH WORSE OUTCOMES

Factor	HR (95% CI)	P-value
TP53 Mutations	3.04 (2.07, 4.48)	**< 0.001**
Therapy-Related MDS	2.54 (1.73, 3.71)	**< 0.001**

- 69 patients transformed to AML at time of or after HMA-F
- mOS from time of AML diagnosis: 3.16 months (95% CI: 2.60, 4.70)

OVERALL SURVIVAL BY FIRST HMA FAILURE THERAPY

- 2 patients directly underwent SCT (mOS 26.14 months) and 6 patients received targeted therapy with mOS not reached
- Otherwise, no difference by treatment regimen
- No difference in mOS observed with:
  - HMA-based therapy, p=0.778
  - Venetoclax-based therapy, p=0.537

CONCLUSIONS

- Patients with HMA-F MDS have high-risk features (poor cytogenetics, adverse mutations, and often therapy-related)
- At the time of HMA-F, patients present with higher BM blasts, worsening thrombocytopenia, and more cytogenetic abnormalities and mutations
- The IPSS-R scoring system can also be used to validate risk at the time of HMA failure
- Higher-risk MDS patients who underwent SCT have significantly improved survival
- Patients with *TP53* mutations and therapy-related MDS have worse overall survival from time of HMA-F

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CONTACT

Kelly Chien and Guillermo-Garcia Manero
kchien@mdanderson.org
ggarciam@mdanderson.org