Clinical Outcome of Myelodysplastic Syndrome Progressing on Hypomethylating Agents with Evolving Frontline Therapies: Continued Challenges and Unmet Needs

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BACKGROUND

- Historically, clinical outcome of patients with myelodysplastic syndrome (MDS), progressing on hypomethylating agents (HMA; Azacitidine or Decitabine) has been dismal with median overall survival (OS) of less than 6 months.
- With recent approval of venetoclax-based combinations for acute myeloid leukemia (AML) and CPX-351 for AML with MDS related changes (primary or secondary), clinical outcome has improved in sub-set of high-risk patients compared to historical cohorts.
- Information on the characteristics, treatment and outcomes of patients after progressing on HMA therapy in recent times is limited. Hence, we report our experience in the current era of novel therapies.

OBJECTIVES

- To determine the clinical outcomes of MDS patients who progressed on HMA-based therapy in the current era of novel therapies.
- To investigate potential prognostic factors associated with these patients' clinical outcomes.

METHODS

- We reviewed the medical records of patients diagnosed with MDS and treated at the Mayo Clinic between February 2015 and February 2021.
- We identified and retrospectively analyzed clinical outcome of 71 patients who progressed on HMA-based therapy.
- We described clinical characteristics of these patients, and we highlighted the treatment modalities and response to treatment received after progressing on HMA-based therapy.
- PFS was defined from the time of post HMA therapy response till progression/ last follow up or death.
- OS was defined from the time of progression after HMA-based therapy to the last follow up or death.
- Cox regression multivariate analysis for OS after progression on HMA-based therapy was also performed.

RESULTS

Table 1: Baseline Patients Characteristics (n=71)

Patient Characteristics	No. (%), or Median [range]
Age, Years	67 [36-91]
Male	44 (62)
R-IPSS Score at Diagnosis	
Low	6 (8)
Intermediate	13 (18)
High	19 (27)
Very High	33 (46)
Therapy-related MDS	17 (24)
BM blasts, %	52 [0-95]
Cytogenetics at diagnosis	
Complex cytogenetics	34 (48)
High risk cytogenetics	40 (56)
HMA prior to progression	
Azacitidine	38 (53)
Decitabine	30 (42)
Azacitidine + investigational agent	3 (4)
Number of HMA cycles	4 [1-20]
History of prior allogeneic stem cell transplantation	5 (7)
Time from MDS diagnosis to HMA progression (months)	10.9 [1.6-79.4]
MDS IPSS-R at HMA progression (n= 23)	
Intermediate risk	5 (22)
High risk	3 (13)
Very High risk	15 (65)
Disease status at progression	
MDS-EB1	9 (14)
MDS-EB2	14 (18)
AML	48 (68)
Mutations at HMA Progression	
TP53	31 (44)
ASXL1	15 (21)
RUNX1	10 (14)
RAS	9 (13)
TET2	8 (11)
SRSF2	5 (7)
BCOR	5 (7)
IDH1 or IDH2	4 (6)
U2AF1	4 (6)
EZH2	4 (6)
CBL	3 (4)
DNMT3A	2 (3)
DDX41	1 (1)
SETB1	1 (1)

Table 2: Treatment modalities and response to treatment (n= 71)

First-line therapy after progression on HMA/ complete response rate [number treated/CR-CRi-mCR rate (%)]	MDS-EB1 n=10		MDS-EB2 n= 13		AML n= 48	
	TP53m n= 3	TP53 wt n= 6	TP53m n= 4	TP53 wt n= 10	TP53m n=24	TP53 wt n= 24
Venetoclax-based therapy (combination with LDAC or HMA)	2/ 50%	3/ 0%	4/ 25%	7/ 43%	12/ 42%	14/ 71%
CPX-351	0	0	0	2/ 0%	4/ 0%	6/ 33%
Other low intensity therapies*	1/ 0%	4/ 25%	0	1/ 0%	1/ 50%	3/ 33%
Best supportive care	0	0	0	0	5/ 0%	0
Intensive chemotherapy (7 + 3 or High dose cytarabine based)#	0	0	0	0	2/ 50%	1/100%

MDS-EB; MDS with excess blast, LDAC; low dose cytarabine, HMA; hypomethylating agent, m; mutated, wt; wild type
* Other low intensity chemotherapy (IDH1/IDH2 inhibitor, Gemtuzumab ozogamicin, ruxolitinib, alternate hypomethylating agent)
# 5 AML patients did not receive induction chemotherapy

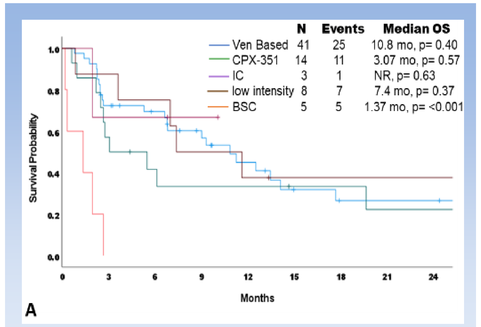


Figure A: Kaplan Meier survival curve after HMA progression based on different therapies

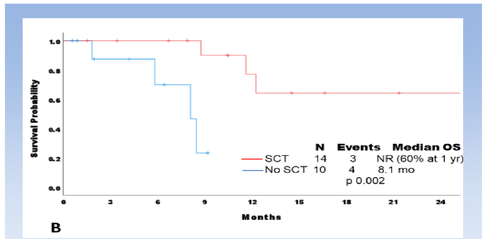


Figure B: Kaplan Meier survival curve of patients with CR receiving SCT vs patient in CR and no SCT

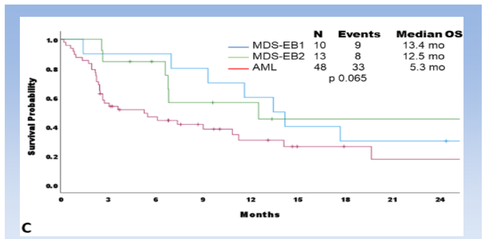


Figure C: Kaplan Meier survival curve after HMA progression in patients with MDS-EB1, MDS-EB2 and AML

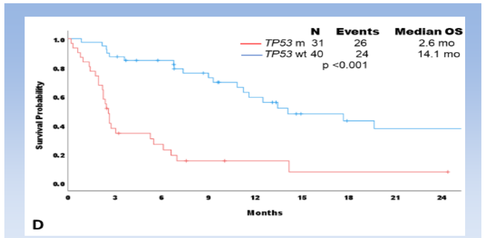


Figure D: Kaplan Meier survival curve after HMA progression in the patients with TP53 mutation

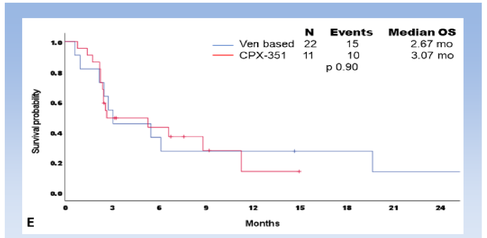


Figure E: Survival of patients with TP53 mutated and/or complex CG receiving HMA/low dose Ara-C + venetoclax vs CPX-351

CONCLUSIONS

- Acknowledging the limitations of retrospective analysis, our report suggests modest improvement in survival of MDS patients progressing on HMA compared to historical data.
- Patients who achieved complete remission after HMA-based therapy retained significance for better OS in multivariate analysis
- Patients who were treated with Venetoclax-based therapy and those who underwent allogeneic stem cell transplantation after achieving remission showed significantly better OS, however it did not retain significance for better OS in multivariate analysis.
- More effective therapies are needed to improve outcome of these high-risk patients.

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Disclosures:

Al-Kali: Astex: Other: Research support to institution; Novartis: Research Funding. **Palmer:** PharmaEssentia: Research Funding; Incyte: Research Funding; Protagonist: Consultancy, Research Funding; CTI BioPharma: Consultancy, Research Funding; Sierra Oncology: Consultancy, Research Funding. **Murthy:** CRISPR Therapeutics: Research Funding. **Litzow:** Pluristem: Research Funding; Actinium: Research Funding; AbbVie: Research Funding; Omeros: Other: Advisory Board; Jazz: Other: Advisory Board; Amgen: Research Funding; Astellas: Research Funding; Biosight: Other: Data monitoring committee. **Foran:** pfizer: Honoraria; takeda: Research Funding; trillium: Research Funding; boehringer ingelheim: Research Funding; syros: Honoraria; sanofi aventis: Honoraria; revolution medicine: Honoraria; servier: Honoraria; bms: Honoraria; certara: Honoraria; abbvie: Research Funding; OncLive: Honoraria; gamida: Honoraria; taiho: Honoraria; novartis: Honoraria; aptose: Research Funding; actinium: Research Funding; kura: Research Funding; h3bioscience: Research Funding; aprea: Research Funding; sellas: Research Funding; stemline: Research Funding. **Badar:** Pfizer Hematology-Oncology: Membership on an entity's Board of Directors or advisory committees.