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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Clinical Implications of *TP53* Mutations/Allelic State in Patients (Pts) with Myelodysplastic Syndromes/Neoplasms (MDS) Treated with Hypomethylating Agents (HMA)- a Multicenter, Retrospective Analysis from the Validate Database

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Introduction

MDS with *TP53* mutations (*TP53* ^{MT}) are associated with high-risk disease features and rapid progression to AML. Effective treatment for this aggressive subtype is still not available. As compared to monoallelic *TP53* ^{MT}, biallelic MT have been associated with adverse outcomes and worse overall survival (OS), but the impact of allelic status on treatment response and OS after HMA therapy are not well established. In this study, we analyzed *TP53* allelic state for a large well annotated cohort of pts with MDS who were treated with HMAs.

Methods

The VALIDATE database includes pts with MDS treated with frontline HMA from 14 specialized centers. Pts were considered to have biallelic *TP53* ^{MT} according to the ICC definition (Arber et al. 2022, Blood) if they meet any of the following: a. two *TP53* ^{MT} (variant allelic frequency [VAF]>10% for each) b. single *TP53* ^{MT} with copy neutral loss of heterozygosity (CN-LOH, available for 308 pts) c. *TP53* ^{MT} with del17p and d. Single *TP53* ^{MT} with VAF >50%. Time to event analyses were estimated using Kaplan-Meier estimator and groups were compared by the log-rank test from the time of HMA initiation. Only higher risk (HR)-MDS pts (IPSS>1 or IPSS-R>3.5) with BM biopsy within 180 days after HMA initiation were assessed for complete response (CR) and overall response rate (ORR) according to the IWG 2023 criteria (Zeidan et al, Blood 2023) (n=480). OS was calculated from time of HMA therapy initiation. This study was supported by an independent research grant from AbbVie.

Results

A total of 816 pts met eligibility and were included in this analysis. Median age was 68 years (IQR: 61-74) and 64% were men. MDS excess blast (EB) 1/2 was the most common MDS subtype (62%). Overall, 78% of the pts were treated with HMA monotherapy (26% decitabine [DEC] and 74% azacitidine [AZA]) and 22% received HMA as part of combination therapy. In total, 40% of the pts underwent allogenic HSCT. Median HMA treatment time was 5 months (mo), IQR:3-11. Median follow up time was 17 mo (IQR:9-31). *TP53* ^{MT} were detected in 253 pts (31%) at time of MDS diagnosis, of whom 153 (60%) pts had biallelic *TP53* ^{MT} and 100 (40%) pts had monoallelic *TP53* ^{MT}. Missense MTs were identified in 80% of pts with monoallelic *TP53* ^{MT}. *TP53* ^{MT}/del17p (33%), *TP53* ^{MT}/CN-LOH (28%), and multiple *TP53* ^{MT} (25%) were the most common combinations in pts with biallelic *TP53* ^{MT}. Pts with *TP53* ^{MT} had higher rates of MDS-EB (74% vs. 61%, p<0.001). Complex karyotype was observed in 112 (73%) pts with biallelic *TP53* ^{MT} and 81 (81%) pts with monoallelic *TP53* ^{MT} (p=0.154). Median number of HMA cycles among pts with *TP53* ^{MT} was 8 (IQR:5-12) and higher compared to pts without *TP53* ^{MT} (5 cycles, IQR:3-9), p=0.032 (**Panel-A).** In a logistic regression model for CR, *TP53* ^{MT} was not associated with probability of achieving CR (1.4, 0.89-2.29). CR rates for pts with biallelic *TP53* ^{MT} (18%) and monoallelic *TP53* ^{MT} (14%) were not significantly different, p=0.37. There were also no significant differences in ORR observed between biallelic *TP53* ^{MT} (59%) and monoallelic *TP53* ^{MT} (54%) pts, p=0.39. Among *TP53* ^{MT}pts treated with HMA monotherapy, pts treated with AZA compared to DEC had similar odds for ORR (OR:1.1, 95%CI: 0.7-1.6)/CR (OR: 0.8, 95%CI: 0.4-1.3) and hazard for OS (HR: 1.1, 0.9-1.4). As expected, the median OS (mo, 95%CI) for pts with *TP53* ^{MT} (12, 10-13) was significantly lower than pts without *TP53* ^{MT} (28, 25-31), p<0.001. Importantly, pts with biallelic *TP53* ^{MT} (11, 9-14) had no significant difference in median OS compared to monoallelic *TP53* ^{MT} (13, 11-17), p=0.268 **(Panel-B).** In a multivariable cox proportional hazard regression model for OS (hazards ratio, 95%CI) adjusted for age (1.0, 0.9-1.0), HSCT (0.4, 0.3-0.4), IPSS-M score (1.2, 1.1-1.3), and complex karyotype (1.4, 1.1-1.8), *TP53* ^{MT} status (1.8, 1.4-2.3) was still associated with OS. However, biallelic *TP53* ^{MT} had comparable risk to monoallelic *TP53* ^{MT} (1.2, 0.9-1.7).

Conclusions

To our knowledge, VALIDATE is the largest database of MDS pts with *TP53* ^{MT} who were treated with HMA. We confirm that *TP53* ^{MT} have significant negative impact on survival, but not on response to HMA therapy. Importantly, we did not observe OS differences between monoallelic and biallelic *TP53* ^{MT}. We also show that the type of HMA monotherapy used does not impact outcome of these pts. Overall, pts with *TP53* ^{MT} have very poor outcomes and are in desperate need of new, effective therapies.

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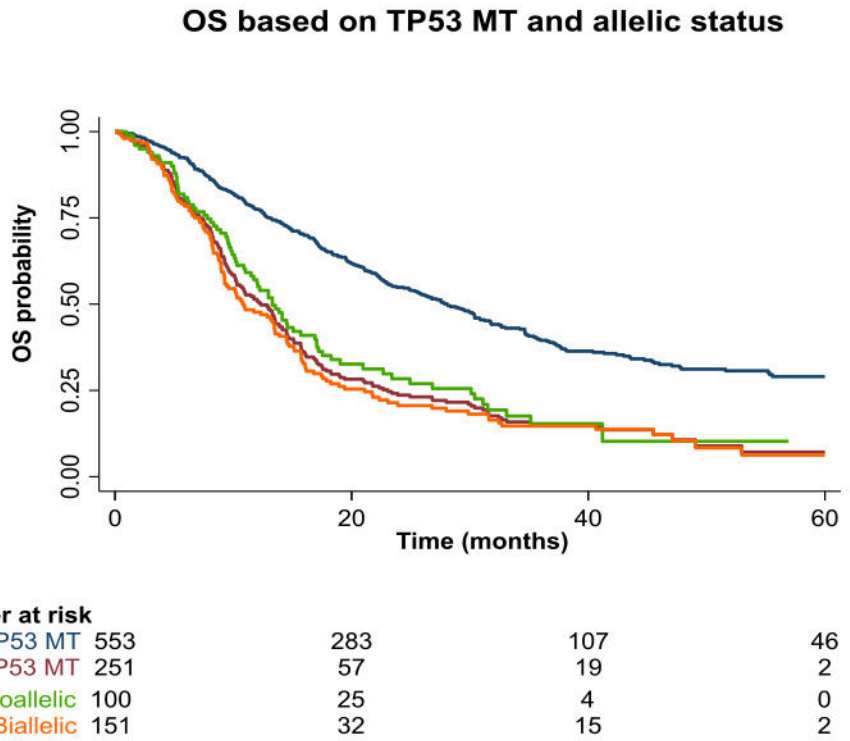
A

Table-1: Patients baseline characteristics by *TP53*^{MT} status

Variable	*TP53*^{MT} N=253	No *TP53*^{MT} N = 563	P-value
Age, year (IQR)	68 (61-74)	69 (61-75)	0.308
Male (%)	157 (62)	376 (67)	0.189
labs			
Hemoglobin, mean (95% CI) g/dl	8.8 (8.6-9.0)	9.2 (9.1-9.4)	0.0006
ANC x10^9/L, mean (95% CI)	1.6 (1.2-2.0)	2.7 (2.2-3.3)	0.009
Platelets x10^9/L mean (95% CI)	69 (60-77)	103 (95-113)	<0.0001
BM Blast, mean (95% CI) %	9 (8-9)	8 (7-8)	0.947
Complex KT	193 (76)	72 (13)	<0.0001
WHO 2016 diagnosis			<0.0001
MDS-SLD	3 (1.2)	25 (4.4)	
MDS-MLD	39 (15.4)	188 (19.2)	
MDS-SLD-RS	1 (0.4)	11 (2.0)	
MDS-MLD-RS	14 (5.5)	37 (6.6)	
MDS-EB	188 (74)	341 (60.6)	
MDS-U	2 (0.8)	28 (5.0)	
MDS-del5q	6 (2.4)	8 (1.42)	
Unknown	0 (0)	5 (0.9)	
Treatment			
Transfusions	110 (44)	195 (35)	0.012
Allogenic HSCT	103 (41)	241 (43)	0.611
HMA treatment			<0.0001
Azacitidine	97 (38)	350 (62)	
Decitabine	59 (24)	108 (19)	
Azacitidine combination	38 (15)	51 (9)	
Decitabine combination	17 (7)	19 (3)	
Other HMA combinations	42 (17)	35 (6)	
Number of cycles (mean, SD)	6 (4)	8 (9)	0.0001
HMA regimen			0.002
Azacitidine 5-days	28 (11)	109 (20)	
Azacitidine 7-days	143 (58)	308 (57)	
Decitabine 5-days	59 (24)	104 (19)	
Decitabine 10-days	11 (5)	7 (1)	
PO decitabine	5 (2)	13 (2)	
Outcomes			
Survival (dead, n)	203 (80)	328 (58)	<0.0001
Progression to AML	117 (45)	181 (32)	0.001

B



A. Patients baseline characteristics by *TP53* mutation (MT) status B. Kaplan-Meier probability estimate of overall survival (OS) for patients stratified by *TP53* MT status and *TP53* MT allelic status (monoallelic vs. biallelic).

Figure 1