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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Comparable Survival of Treatment Naïve *TP53* Mutated Acute Myeloid Leukemia Treated with Hypomethylating Agent Compared to Hypomethylating Agent Plus Venetoclax Based Therapy

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Background

TP53-mutated (m) acute myeloid leukemia (AML) is an adverse risk disease, which continues to have dismal outcome in the contemporary era of novel therapies. Venetoclax (VEN) in combination with hypomethylating agents (HMA; azacitidine or decitabine) have shown to improve complete remission (CR) rates compared to HMA alone, however no significant differences in overall survival (OS) have been observed.

Methods

We conducted a retrospective study through the COMMAND consortium (a collaboration of acute leukemia experts from 10 US academic institutions) to analyze the impact on survival outcomes of HMA plus (+) VEN compared to HMA-based therapies in adult (≥18 years) pts with *TP53*m AML. The AML Database of 381 pts with *TP53*m AML diagnosed between 2012-2022 was queried and 154 (40%) (HMA [n=50] and HMA +VEN [n=104]) pts were identified eligible for this analysis. Continuous variables were summarized as median (range) while categorical variables were reported as frequency (percentage). The Kaplan-Meier method was used to estimate OS, defined as time from diagnosis to death or last follow-up. Logistic regression models were used to determine the univariate and multivariate of OS. Multivariable models included all significant univariate predictors. All tests were two-sided with a *p* value <0.05 considered statistically significant.

Results

Baseline characteristics and responses
The median age (years [yrs]) was 74 (range [R], 38-87) and 71 (R,29-88) yrs in the HMAand HMA + VEN groups (gps) (p= 0.23), respectively (**Table 1**). Thirty-four (68%) and 57 (55%) patients (pts) were ≥ 70 yrs in the HMA and HMA + VEN gps, respectively (p= 0.16). Twenty-six percent vs 31% (*p*=0.57), 86% vs 90% (*p*=0.58) and 68% vs 73% (*p*=0.56) of pts had secondary AML, had complex cytogenetics (CG), and had multi-hit *TP53*m in the HMA and HMA + VEN gps, respectively. The proportion of pts with most frequently occurring (> 5%) myeloid co-mutations (*RUNX1, ASXL1, TET2, DNMT3A, RAS, PTPN11* and *JAK2*) were not significantly (NS) different between the HMA and HMA + VEN gps, as shown in Table 1. The early treatment related mortality in first 30 days of induction was higher in the HMA+VEN gp (25%) when compared with the HMA gp (6%), *p*=0.004.

The complete remission rates (CR/CRi) were higher in the HMA + VEN gp compared to the HMA gp (35% vs 18%, *p*=0.05). Similarly, the proportion of pts receiving allogeneic stem cell transplant (allo-HCT) after induction was higher in the HMA + VEN gp when compared with the HMA gp (13% vs 4%; *p*=0.14).

Duration of response and overall survival

The median follow up was 9.8 months (mo) (R, 1-56) and 5.80 mo (R, 1-30.4) in the HMA and HMA + VEN gps, respectively (*p*=0.12). The median duration of response (DOR) was higher in the HMA +VEN gp (15.6 mo) when compared with the HMA gp (7.93 mo), but NS (*p*=0.26). The median OS was NS different when comparing the HMA and HMA + VEN gps (9.23 vs 7.3 mo, *p*=0.80 [**Figure 1**]).

Multivariable analysis for duration of response and overall survival

We did multivariable analysis (MVA) for DOR and OS using baseline variables (**Table 1**) that showed significance/trend towards significance in univariate analysis (*p*<0.1).

Allo-HCT (HR; 0.11, 95% CI: 0.02-0.52, *p*=0.005) retained significance for better DOR, whereas age $\geq$ 70 yrs (HR; 1.7, 95% CI: 0.63-4.65, *p*=0.28) and complex CG (HR; 3.05, 95% CI: 0.79-11.73, *p*=0.10) did not retain significance in MVA.

In MVA for OS, achievement of CR/CRi (HR; 0.35, 95% CI; 0.20-0.59, *p*=<0.001) and allo-HCT after induction (HR; 0.06, 95% CI; 0.09-0.46, *p*=0.007) retained favorable significance for OS, whereas complex CG (HR; 2.36, 95% CI: 1.11-4.99, *p*=0.02) retained significance for shorter OS. *PTPN11*m (HR; 1.57, 95%CI: 0.75-3.28, *p*=0.23) and *TET2*m (HR; 1.02, 95% CI: 0.56-1.87, *p*= 0.92) did not retain significance in MVA.

Conclusion

In this multi-center real-world study, while HMA+VEN led to improvement in CR rates and a higher proportion of pts were bridged to allo-HCT, it did not associate with an improvement in OS when compared with HMA monotherapy. More effective treatment strategies are warranted to improve outcome of pts with *TP53*m AML.

Variables	HMA N= 50	HMA + VEN N=104	p value
Age in years (median)	74 [38-87]	71 [29-88]	0.23
Age > 70 years	34 (68)	57 (55)	0.16
Gender (male)	24 (48)	66 (64)	0.08
Secondary AML	13 (26)	32 (31)	0.57
Therapy related	18 (36)	31 (30)	0.46
WBC (10³/L)	2.36 [0.56-96.5]	2.63 [0.40-460]	0.86
BM blast (%)	30 [12-90]	32 [7-99]	0.28
PB blast (%)	8 [0-90]	14 [0-92]	0.63
Complex CG	43 (86)	94 (90)	0.58
Multi-hit *TP53*	34 (68)	76 (73)	0.56
Co-mutations (> 5% overall)			
RUNX1	5 (10)	3 (3)	0.10
ASXL1	8 (16)	7 (7)	0.07
TET2	7 (14)	9 (9)	0.26
DNMT3A	8 (16)	6 (6)	0.06
RAS	3 (6)	7 (7)	>0.99
PTPN11	2 (4)	7 (7)	0.72
JAK2	2 (4)	5 (5)	>0.99
Complete remission (CR or CRi)	9 (18)	36 (35)	0.05
Treatment related mortality in 1ˢᵗ 30 days	3 (6)	26 (25)	0.004
Allo-HCT	2 (4)	13 (13)	0.14

HMA; hypomethylating agent, VEN; venetoclax, CG; cytogenetics, BM; bone marrow, allo-HCT; allogeneic stem cell transplantation
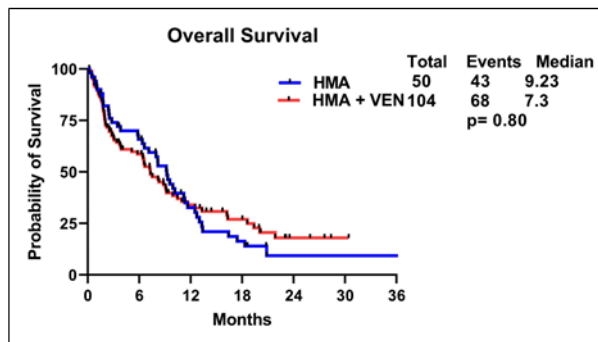

Figure 1