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Association of leukemia genetics with response to venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia

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Venetoclax (ABT-199) is a selective inhibitor of BCL-2 that has demonstrated impressive activity in AML when combined with hypomethylating agents (HMA). As frontline combination therapy, venetoclax and HMA (VEN-HMA) produced an encouragingly high complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate of 67%.[1] The activity of VEN-HMA was also reported in advanced AML outside of clinical trials,[2] with the combination showing promising activity even in poor prognostic subtypes of AML, but experience in this setting is limited.

We retrospectively analyzed the outcomes of a cohort (n = 90) of adults with r/r AML who were treated at our institution outside clinical trials with VEN-HMA from October 2016 and March 2019. We analyzed the association between response to therapy and leukemia-associated mutations, cytogenetics, and other pertinent patient and leukemia-related features.

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Authorship contributions

IA and VP designed research; all authors collected, assembled, analyzed, and interpreted data; IA, JFS, and VP wrote the manuscript; and all authors approved the final version.

Disclosure of conflict of interest

IA has served on advisory boards with Agios is member of the speakers' bureau with Jazz Pharmaceuticals. A. Salhotra has served as consultant for Kadmon Corporation. RN has served on advisory boards with Merck and Celgene and has a research collaboration with Jazz Pharmaceuticals. A. Stein serves on the speakers' bureau for Amgen and Celgene. VP has served on the advisory boards for Abbvie and Jazz pharmaceuticals and is member of speakers' bureau for Jazz Pharmaceuticals, Amgen, Novartis and Abbvie. The remaining authors have no relevant conflicts of interest to declare.

We restricted our analysis to evaluable patients who had completed at least one cycle (4 weeks) of the combination therapy and received an end-of-treatment assessment of response. Genetic risk stratification was based on the 2017 European LeukemiaNet (ELN) combined cytogenetic and molecular profile.[3] The majority of mutation analyses were done at our institution using a next generation sequencing (NGS) panel (Supplemental Table 1). Cases were also classified on the basis of genetic alterations in functional pathways as described previously.[4]

Response (CR/CRi) was the primary endpoint. Overall survival (OS) and leukemia-free survival (LFS) were secondary endpoints. Descriptive statistics were used for baseline characteristics. The Fisher's exact test and log-rank test were used to explore the differences in tumor response and OS or LFS by characteristics. Multivariable logistic regression and Cox regression models were used to evaluate the independent effects of genetic mutations on outcomes when adjusting for baseline characteristics. Baseline characteristics that were significantly associated with outcomes at 0.1 level were included in the multivariable models. All tests were two-sided at a significance level of .05. All analyses were performed using the SAS statistical package version 9.4 (SAS Institute, Cary, NC, USA) and the rpart function of R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

The median age of patients was 59 years (range: 18–81). AML was considered *de novo* in 58 (64%) patients, therapy-related in 10 (11%) patients, and secondary in 22 (24%) patients. Forty-six (51%) patients had prior exposure to HMA. The median number of prior lines of therapy before initiating VEN-HMA was 2 (range: 1–8), and 26 (29%) patients were treated for relapse after allogeneic hematopoietic cell transplantation (alloHCT). Patient characteristics are shown in Table 1.

The majority of patients had ELN adverse- (66%) or intermediate-risk (26%) AML. The most commonly detected mutations in this cohort were *FLT3-ITD/TKD* (27%), *RUNX1* (22%), *IDH1/2* (17%), *RAS* (16%), *TP53* (14%), *DNMT3A* and *ASXL1* (13% each). Genetic alterations are depicted in Supplementary Tables 2 and 3.

The majority of patients received venetoclax in combination with decitabine (n = 81, 90%), while only 9 (10%) patients received venetoclax in combination with 5-azacitidine. For patients who received decitabine, cycle 1 was given as a 10-day course in 48 (59%) patients, whereas 33 (41%) patients received a 5-day course.

The response rate (CR/CRi) was 46% (n = 41), including 23 (26%) CR and 18 (20%) CRi. For the 36 patients who achieved CR/CRi and also had MRD assessment available at the time of best response, 23 (64%) were MRD-negative. The best response was observed after a median of 1 (range: 1–3) cycle for patients attaining CR/CRi, with 24 (59%) responders achieving CR/CRi after only one cycle. Fourteen (34%) responders were able to undergo alloHCT after attaining CR/CRi with VEN-HMA.

In univariate analysis, only ELN cytogenetic risk influenced the rate of CR/CRi, with better response observed in favorable and intermediate-risk compared with adverse-risk genetic groups (75% vs. 65% vs. 34%, $P = 0.004$). Among various AML mutations, *TET2* mutation was associated with a better response to VEN-HMA (*TET2*+ vs. *TET2*−; 86% vs. 39%,

P = 0.038) (Supplementary Table 2). There was a suggestion of lower response rate for *U2AF1* mutation (none of the 5 patients carrying the mutation responded). The activity of VEN-HMA was observed across all functional subgroups of AML, and the CR/CRi rate was not significantly different according to the presence or absence of alterations in specific functional pathways (Supplementary Table 3).

In multivariate analysis including common (incidence >7%) mutations and genetic pathway alterations as well as clinical/cytogenetic features, only ELN genetic risk (OR: 0.25; 95% CI: 0.09–0.67) was independently associated with reduced CR/CRi, while the presence of either *ASXL1* (OR: 4.88; 95% CI: 1.02–25.67, *P* = 0.029) or *TET2* (OR: 12.21; 95% CI: 1.19–636.50, *P* = 0.023) mutations were independently associated with better CR/CRi (Supplementary Table 4).

The median follow up was 15.8 months (range: 0.8–27.7) for all patients and 9.8 for surviving patients. The median OS for all patients was 7.8 months (95%CI: 5.9–15.5), and it was 16.6 months (95%CI: 13.5–26.8) for patients who achieved CR/CRi versus 5.1 months (95%CI: 3.4–6.6) for patients who did not respond (*P* < .001). Only AML subtype (*de novo* vs. secondary vs. therapy-related) and ELN genetic risk independently predicted OS for patients treated with VEN-HMA in multivariate analysis. Patients with *de novo* AML had better OS compared to that associated with t-AML (HR= 1.33; 0.55–3.23) and secondary AML (HR= 3.00; 1.58–5.70) (*P* = 0.004). Similarly, AML with adverse-risk genetic alterations was associated with worse OS compared to favorable-/intermediate-risk AML (HR= 2.02; 1.11–3.69, *P* = 0.022). In univariate analysis for mutations and genetic functional pathways, the presence of *TP53* mutation (P = 0.049) and alteration in chromatin modifying genes (P =0.002) adversely influenced OS; however, in multivariate analysis neither independently predicted OS (Supplemental Table 5, Supplementary Figure 1).

The median LFS for patients who achieved CR/CRi with VEN-HMA was 8.9 months (95%CI: 5.9–15.2). None of the clinical or cytogenetic characteristics impacted LFS for this cohort. Among somatic mutations and genetic pathways, only *TP53* mutation was associated with reduced LFS in univariate analysis (*P* = 0.01), but in multivariate analysis statistical significance was lost (*P* = 0.074) (Supplemental Table 5).

Here we describe the largest cohort of r/r AML patients treated with VEN-HMA whose leukemia was characterized for genetic alterations, and we have shown marked activity for the combination regardless of traditional clinical and genetic factors. Our data show that this combination has activity across a variety of cytogenetic and molecular subtypes of AML. Responses were often deep, as around two-thirds of evaluable responders in this cohort attained MRD negativity. Furthermore, a proportion of these r/r patients were able to successfully undergo alloHCT with curative intent. Certain conventional predictors of poor response including failure of prior HMA therapy or receipt of prior alloHCT were not predictive of a poor CR rate in our cohort. However, response and survival rates were higher among favorable- and intermediate-risk genetic subgroups compared to those in the adverse-risk genetic group, confirming the usefulness of the ELN risk stratification when applied to patients treated with this combination as well.

Both *TET2* and *ASXL1* mutations were associated with improved response to VEN-HMA therapy in r/r AML in our cohort, and this finding could be related to the sensitivity of AML carrying these mutations to HMA in general.[5,6] Prior studies have linked the *TET2* mutation with response to HMA,[5,6] but interestingly in one study the response was more pronounced in the absence of the *ASXL1* mutation.[5] In another study, the *TET2* mutation predicted better response to HMA, but the *ASXL1* mutation predicted better OS with HMA treatment.[6] The favorable response in *ASXL1* mutated patients is surprising in our cohort, but the impact of the *ASXL1* mutation may be modulated by other coexisting mutations. High-risk mutations such as *TP53* and *FLT3* predict resistance to chemotherapy, but in this cohort of r/r AML both of these mutations were associated with similar responses to VEN-HMA compared to other mutations.

Notwithstanding the limitations of small numbers of individual genetic alterations as well as the retrospective nature, we show that VEN-HMA therapy is effective across various genetic and clinical risk groups of r/r AML. This regimen therefore represents the preferred choice for unfit patients as well as for patients who are unlikely to benefit from standard salvage treatments because of factors such as relapse after alloHCT and/or high-risk genetics such as complex cytogenetics, monosomal karyotype, or *TP53* mutation. There may be opportunities to add novel agents to this well-tolerated backbone in order to further enhance response and improve outcome of r/r AML, particularly for adverse risk subsets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Patient characteristics and CR/CRi rate. Abbreviations: allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; HMA, hypomethylating agents; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; R/R, relapsed/refractory, CR, complete remission, CRi, CR with incomplete count recovery

	Number (%)	CR/CRi rate	P-value
Median Age (range)	59 (18–81)		
Age			
≥ 60	44 (49)	24 (55)	0.14
< 60	46 (51)	17 (37)	
Sex			
Male	46 (51)	18 (39)	0.29
Female	44 (49)	23 (52)	
AML type			
De novo	58 (64)	29 (50)	0.36
Therapy-related	10 (11)	5 (50)	
Secondary	22 (24)	7 (32)	
MDS	11 (50)		
MPN	7 (32)		
MDS/MPN	4 (4)		
2017 ELN Genetics Risk			
Favorable/Intermediate	31 (34)	21 (68)	0.004
Adverse	59 (66)	20 (34)	
Prior allo-HCT			
Yes	26 (29)	12 (46)	1.00
No	64 (71)	29 (45)	
Prior HMA			
Yes	46 (51)	19 (41)	0.53
No	44 (49)	22 (50)	
Prior lines of therapy			
Median (range)	2 (1–8)		
≤ 2	57 (63)	29 (51)	0.20
>2	33 (37)	12 (36)	
HMA type and duration in combination with venetoclax			
Azacitadine	9 (10)	3 (33)	0.78
Decitabine	81 (90)	38 (47)	
5 days	33 (41)	15 (46)	
10 days	48 (59)	23 (48)	

*Based on chi-square or Fisher's exact test whenever appropriate