HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Letter
Open Access

Genotype and Intensive Pretreatment Influence Outcome of Acute Myeloid Leukemia Patients Treated With Venetoclax in Combination With Hypomethylating Agents or Low-dose Cytarabine: "Real World" Data From Germany

Krischan Braitsch[1], Laura K. Schmalbrock[2,3], Paul Jung[2], Irmgard Bumeder[4], Philipp Kiewe[5], Judith S. Hecker[1], Mareike Verbeek[1], Jörg Westermann[6], Lars Bullinger[3,6,7], Ulrich Keller[2,7], Florian Bassermann[1,7,8], Jan Krönke[2], Katharina S. Götze[1,7,8], Kathrin Rieger[2]

Correspondence: Kathrin Rieger (kathrin.rieger@charite.de).

The B-cell lymphoma-2 inhibitor venetoclax (VEN) combined with hypomethylating agents (HMA) or low-dose cytarabine (LDAC) has shown encouraging results in acute myeloid leukemia (AML) patients older than 75 years or unfit for intensive therapy.[1,2] Despite the promising results of VEN and HMA/LDAC combinations as frontline treatment, the identification of patients who benefit most is still under discussion. Especially patients with *IDH1/2* and *NPM1* mutations were reported to benefit from this treatment combination.[1–4] In relapsed/refractory (r/r) AML patients and particularly after prior HMA treatment, the impact on previous treatment on response is still discussed controversially.[5,6] As European Medicines Agency approval was given only recently in 2021, VEN + HMA/LDAC was often used "off-label" in European countries after failure to prior treatment and mostly added to HMA treatment after health insurance approval. To investigate outcomes of VEN treatment in combination with HMA/LDAC in this setting, we conducted a retrospective study of 73 AML patients treated between 2017 and 2021 at 2 university hospital sites and 2 large outpatient centers in Berlin and Munich, Germany.

We analyzed baseline clinical and molecular characteristics as reported in medical charts and local laboratories. All patients who had received at least 1 VEN dose were included in this study. Written informed consent to analysis of their records for scientific purposes was given by all patients. Detailed information on definition of treatment lines, VEN administration as well as data collection and statistical methods are described in the Suppl. Appendix.

The median age of the cohort at the beginning of VEN treatment was 73 (20–85) years. Most patients had secondary (s) AML (n = 34 [47%]) and were assigned to the ELN2017[7] adverse risk group (n = 32 [49%]; favorable n = 12 [18%]; intermediate n = 22 [33%]; missing information n = 7 patients). A normal karyotype was present in n = 35 of 64 (55%) patients; *NPM1* mutations were present in n = 13 of 66 (20%) patients and n = 9 of 65 (14%) were *FLT3*-ITD positive. *IDH1/2* mutations were found in n = 19 of 57 (33%) patients (Table 1). The median time of follow-up was 8.3 months. Fifteen (21%) patients received VEN as first-line treatment, of which n = 13 started HMA treatment before VEN was added due to delayed health insurance approval. The other n = 58 (79%) patients received VEN after at least 1 prior treatment line (1 pretreatment n = 25 [34%]; 2 pretreatments n = 12 [16%]; ≥3 pretreatments n = 21 [29%]). First-line treatment in r/r patients consisted of intensive chemotherapy (n = 36 [47%]), including n = 26 (36%) patients who underwent allogeneic stem-cell transplantation (allo-HSCT); n = 25 (34%) patients had received >4 cycles of HMA treatment before VEN combination.

Due to pending health insurance approval in all cases, VEN was added delayed to HMA/LDAC treatment in the majority

[1]Department of Medicine III, Technical University Munich, Klinikum Rechts der Isar, Munich, Germany
[2]Department of Hematology, Oncology and Cancer Immunology, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany
[3]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Germany
[4]Praxis und Tagesklinik für Hämatologie und internistische Onkologie, Munich, Germany
[5]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, Germany
[6]Department of Hematology, Oncology and Tumor Immunology, Campus Virchow Clinic, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany
[7]German Cancer Consortium (DKTK), Partner Sites Berlin/Munich, German Cancer Research Center (DKFZ), Heidelberg, Germany
[8]Bavarian Cancer Research Center (BZKF), Partner Site Munich, Germany
KB, LKS, KSG, and KR have contributed equally to this work.
Supplemental digital content is available for this article.

HemaSphere (2022) 6:9(e759).
http://dx.doi.org/10.1097/HS9.0000000000000759.
Received: March 24, 2022 / Accepted: July 3, 2022

Table 1

Baseline Clinical Characteristics

Parameter	Value
Age at VEN start	
Years median (range)	73 (20–85)
Sex, n (%)	
Male	42 (58)
Female	31 (42)
Type of AML, n (%)	
De novo	30 (41)
sAML	34 (47)
tAML	9 (12)
Risk group ELN2017, n (%)	
Favorable	12 (18)
Intermediate	22 (33)
Adverse	32 (49)
na	7
Cytogenetics, n (%)	
Normal karyotype	35 (55)
Complex karyotype	13 (20)
Other	16 (25)
na	9
Molecular marker, n (%)	
NPM1 mutated[a]	13 (20)
FLT3-ITD positive[b]	8 (14)
IDH1/2 mutated[c]	19 (33)
Number treatment lines, n (%)	
0	15 (21)
1	25 (34)
2	12 (16)
≥3	21 (29)
Previous treatments, n (%)	
Intensive treatment	36 (49)
Allo-HSCT	26 (36)
HMA/LDAC treatment	57 (78)
HMA/LDAC >4 cycles	25 (34)

[a]Information available for n=64 patients.
[b]Information available for n=65 patients.
[c]Information available for n=57 patients.
Allo-HSCT = allogeneic stem-cell transplantation; AML = acute myeloid leukemia; HMA = hypomethylating agents; LDAC = low-dose cytarabine; sAML = secondary AML; tAML = therapy-related AML; VEN = venetoclax.

of patients: In first-line patients (n = 15), VEN was started on day 1 in n = 2 (3%), added during cycle 1 of HMA/LDAC treatment in n = 1 (1%) patients or started after cycle 1 of HMA/LDAC in n = 9 (12%) patients. Three (4%) patients received VEN after 2 cycles of HMA/LDAC. In r/r patients, VEN was added to HMA/LDAC during cycle 1 in n = 17 (23%) patients; n = 5 (7%) patients received VEN combination after 1 cycle of HMA/LDAC and n = 32 (44%) patients after ≥2 cycles HMA/LDAC (not available for n = 4 patients).

The median VEN dosage after ramp-up at therapy initiation in all patients was 400 mg (50–800 mg). Azacytidine was the most common combination partner (n = 34 [47%]), followed by LDAC (n = 20 [28%]) and decitabine (n = 18 [25%]; information not available for n = 1 patient). At the beginning of VEN treatment, n = 49 of 67 (73%) patients had severe neutropenia (<500/nL). Antimicrobial prophylaxis was given in n = 13 of 66 (20%) and antifungal azole prophylaxis in n = 22 of 62 (35%) of the patients, respectively.

At the time of data cut-off, VEN treatment was ongoing in n = 12 (16%) of patients. Patients completed a median of 3 (0–17) cycles of VEN and the median period of VEN treatment was 110 days (3–798). A total of n = 20 (27%) patients received reduced VEN doses at the beginning or during cycle 1, and in n = 19 (26%) patients, VEN dose was adjusted during the following treatment cycles. Six patients with r/r AML underwent allo-HSCT after VEN combination treatment.

Response assessment was available for n = 58 patients, of which n = 10 (17%) received VEN combinations as first-line treatment and n = 48 (83%) after failure to previous treatments. The overall response rate (ORR) in our study cohort was 49% (complete remission/CR with incomplete count recovery [CR/CRi] n = 19 [33%]; partial remission [PR] n = 9 [16%]; stable disease [SD] n = 14 [24%]; refractory disease [RD] n = 16 [28%]), which was lower compared to prospective trials reporting CR/CRi rates >65% in elderly treatment naive AML patients,[1,2] but comparable to studies focused on r/r AML patients,[3,5,8,9] demonstrating that VEN combinations are a feasible treatment option in this clinical setting. ORR was significantly better in patients harboring *NPM1* and/or *IDH1/2* mutations (ORR 87% vs 33%, $P < 0.01$; Suppl. Figure S1), which due to the cohort size of this study and co-mutational pattern in n = 3 patients, were analyzed as one group. In congruence with our findings, both were associated with superior outcome to VEN combination treatment in previous reports.[2,3,6,9,10] In contrast, age (≥65 years), *FLT3* mutations, patients with complex karyotype or *TP53* mutation as well as prior treatment (allo-HSCT, number of treatment lines, HMA treatment, intensive therapy) had no significant influence on response. The observation that ORR in our study cohort was not influenced by prior HMA treatment is an important finding, as the influence of HMA treatment on response has been discussed controversially in previous studies. DiNardo et al[9] and Feld et al[6] showed a particularly worse response rate in patients with previous HMA treatment, while other studies found no impact of prior HMA administration on treatment response.[3,5] Although 15 patients in our cohort were considered as treated first-line with VEN combination, only n = 2 actually received VEN at the beginning of the intended combination treatment. Delay of VEN initiation can be explained by the "off-label" indication of VEN requiring approval from insurance agencies before administration due to reimbursement issues. All other patients were exposed to LDAC/HMA before VEN initiation, which might explain differences seen here to studies that reported a negative impact of previous LDAC/HMA treatment.

The median OS of the entire cohort was 6.5 months. OS was significantly longer in patients achieving CR/CRi/PR compared with SD/RD patients ($P < 0.01$; Figure 1A). With respect to prior treatment, we found that OS was significantly shorter in patients who had received ≥2 treatment lines ($P = 0.01$; Figure 1B) before VEN, of which the majority (n = 28/33 [85%]) had received intensive therapy. This is in line with a previous study from Stahl et al[3] demonstrating a worse OS after ≥3 salvage treatments. These observations suggest that certain patients may benefit from earlier VEN combination treatment and studies investigating VEN in combination with intensive first-line and salvage regimens are currently ongoing. While prior HMA treatment had no impact on OS in pretreated patients, we observed a significantly shorter OS in patients who had received intensive therapy ($P = 0.03$, Suppl. Figure S3D) and allo-HSCT ($P = 0.05$; Figure 1C), which is congruent with studies reporting a negative impact of allo-HSCT on outcome to VEN combination treatment.[3,11] In a multivariate analysis, allo-HSCT was the only pre-treatment variable that negatively impacted OS (hazard ratio [HR] = 2.70, 95% confidence interval [CI] = 1.07–6.81, $P = 0.04$; Suppl. Figure S2) in our study cohort, with a very poor OS of median 3.9 months. The very low CR/CRi rate of 20% in allo-HSCT patients in our study cohort was comparable to results from Piccini et al.[11] However, better CR/CRi rates between 30% and 40% were reported after allo-HSCT in 2 other studies.[12,13] Interestingly, allo-HSCT had no impact on response rates. Of note, n = 4 patients with r/r AML responded to VEN combination therapy and subsequently underwent allo-HSCT.

Furthermore, OS was significantly longer in *NPM1* and/or *IDH1/2* mutated patients as compared to other genetic alterations ($P = 0.02$; Figure 1D), which was confirmed by multivariate analysis (HR = 0.35, 95% CI = 0.15–0.83, $P = 0.02$).

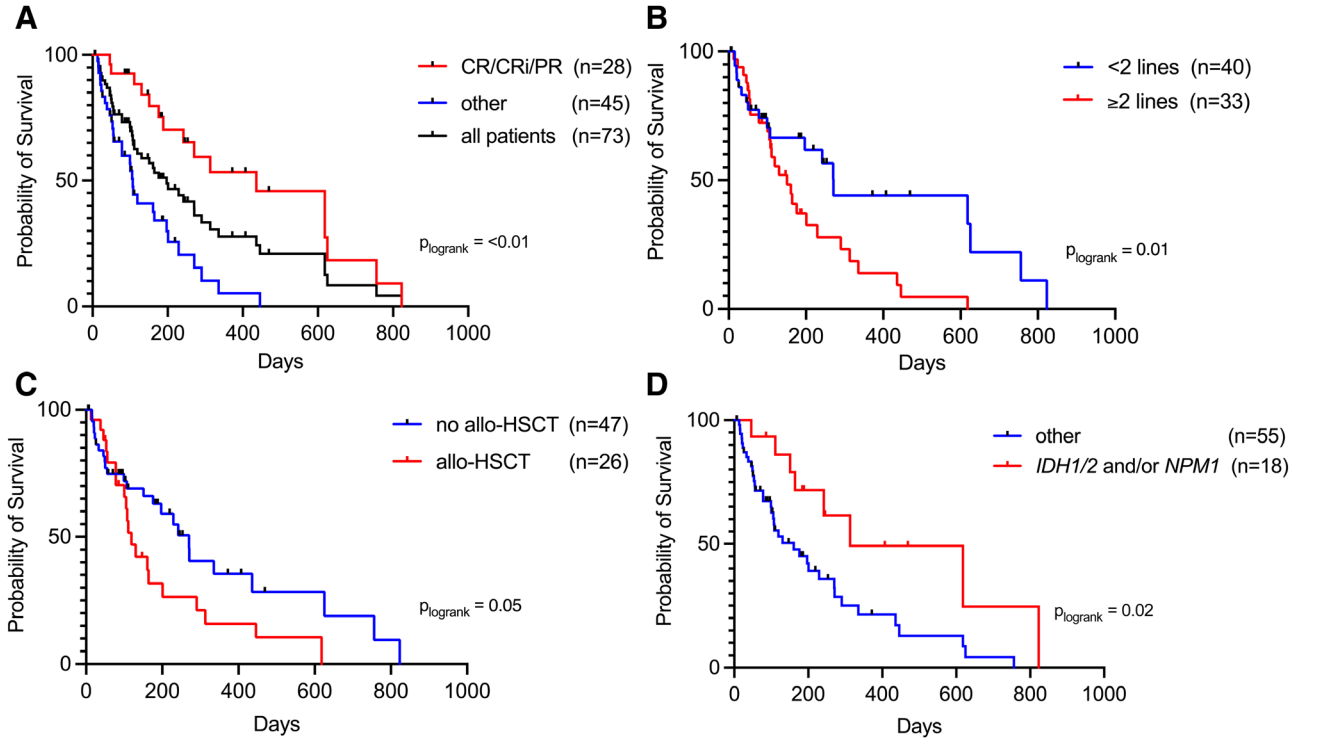

Figure 1. Survival curves. OS (n = 73 patients) was significantly longer in patients (A) achieving response (CR/CRi/PR) to VEN combination treatment, (B) pretreated with less than 2 prior treatment lines, (C) who had not previously received allo-HSCT, (D) harboring an *NPM1* and/or *IDH1/2* mutation. Allo-HSCT = allogeneic stem-cell transplantation; CR = complete remission; CRi = CR with incomplete count recovery; OS = overall survival; PR = partial remission; VEN = venetoclax.

This finding is comparable with a study from Lachowiez et al[10] that reported a particularly superior outcome for older, *NPM1* mutated patients after first-line HMA + VEN therapy, compared with HMA treatment alone or intensive chemotherapy. This underscores the importance of molecular characterization to identify patients who benefit most from this treatment combination including relapsed patients. There was no significant impact on OS with regard to age at the time of VEN initiation, ELN2017 risk group and AML type.

"Real-world" data reflect outcomes in clinical settings which can differ from those reported in clinical trials[14,15] and thus contribute to a better understanding of drug efficacy. Our data show that VEN in combination with HMA or LDAC is an effective treatment with high response rates even in elderly patients with r/r AML. This was especially noted in patients harboring *NPM1* and/or *IDH1/2* mutations. Of note, the number of r/r patients with failure to previous treatment was high (n = 58 [79%]), representing the majority of this cohort. Survival and response rates seem to be worse in intensively pretreated patients and remain dismal in patients with relapse after allo-HSCT. Larger cohorts from clinical trials and "real-world" settings are needed to identify the r/r AML patients that benefit most from VEN combinations.

AUTHOR CONTRIBUTIONS

KSG, KR, JK, KB, and LKS designed the study, interpreted data, and drafted the manuscript. LKS, KB, PJ, IB, PK, JSH, MV, JW, LB, UK, and FB contributed to data collection and PJ, IB, PK, JSH, MV, JW, LB, UK, and FB revised the manuscript critically. KB, LKS, and PJ performed literature research. KB and LKS analyzed data and performed statistical analysis. All authors have reviewed and approved the manuscript.

DISCLOSURES

LKS is a participant in the Berlin Institute of Health–Charité Clinician Scientist Program funded by the Charité –Universitätsmedizin Berlin and the Berlin Institute of Health. LKS received travel funding from Gilead. KB received honorarium from Bayer. JW received honoraria from BMS and Astellas, declares consultancy and honoraria from Novartis, Amgen, Abbvie, Pfizer, Sanofi and Stem Cell Line. LB received honoraria from Seattle Genetics, Sanofi, Astellas, Amgen, consultancy fee from Gilead, Hexal, and Menarini, consultancy fee and Honoraria Abbvie, BMS/Celgene, Daiichi Sankyo, Janssen, Jazz Pharmaceuticals, Novartis and Pfizer, and research funding from Bayer and Jazz Pharmaceuticals. UK declares advisory role for Abbvie. JK declares advisory board role for Abbvie and BMS/Cellgene. KSG declares advisory board role for Abbvie and BMS/Celgene, and research funding from BMS/Celgene. KR declares consultancy and honoraria from Roche, BMS, Amgen, Novartis, Jannssen-Cilag and Abbvie. All the other authors have no conflicts of interest to disclose.

REFERENCES

1. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135:2137–2145.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617–629.
3. Stahl M, Menghrajani K, Derkach A, et al. Clinical and molecular predictors of response and survival following venetoclax therapy in relapsed/refractory AML. *Blood Adv*. 2021;5:1552–1564.
4. Aldoss I, Zhang J, Mei M, et al. Venetoclax and hypomethylating agents in FLT3-mutated acute myeloid leukemia. *Am J Hematol*. 2020;95:1193-1199.
5. Aldoss I, Yang D, Aribi A, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Haematologica*. 2018;103:e404–e407.
6. Feld J, Tremblay D, Dougherty M, et al. Safety and efficacy: clinical experience of venetoclax in combination with hypomethylating agents in both newly diagnosed and relapsed/refractory advanced myeloid malignancies. *HemaSphere*. 2021;5:e549.
7. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.

8. Aldoss I, Yang D, Pillai R, et al. Association of leukemia genetics with response to venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Am J Hematol*. 2019;94:E253–E255.
9. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol*. 2018;93:401–407.
10. Lachowiez CA, Loghavi S, Kadia TM, et al. Outcomes of older patients with NPM1-mutated AML: current treatments and the promise of venetoclax-based regimens. *Blood Adv*. 2020;4:1311–1320.
11. Piccini M, Pilerci S, Merlini M, et al. Venetoclax-based regimens for relapsed/refractory acute myeloid leukemia in a real-life setting: a retrospective single-center experience. *J Clin Med*. 2021;10:1684.
12. Joshi M, Cook J, McCullough K, et al. Salvage use of venetoclax-based therapy for relapsed AML post allogeneic hematopoietic cell transplantation. *Blood Cancer J*. 2021;11:49.
13. Byrne M, Danielson N, Sengsayadeth S, et al. The use of venetoclax-based salvage therapy for post-hematopoietic cell transplantation relapse of acute myeloid leukemia. *Am J Hematol*. 2020;95:1006–1014.
14. Winters AC, Gutman JA, Purev E, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. *Blood Adv*. 2019;3:2911–2919.
15. Morsia E, McCullough K, Joshi M, et al. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. *Am J Hematol*. 2020;95:1511–1521.