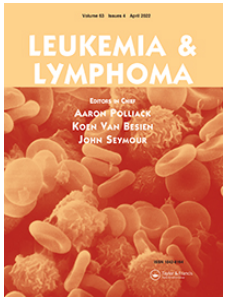

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ORIGINAL ARTICLE

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Venetoclax in combination with hypomethylating agents or low dose cytarabine for relapsed and refractory acute myeloid leukemia

Molly E. Graveno[a#], Alison Carulli[a], Craig W. Freyer[a], Brendan L. Mangan[a], Robert Nietupski[b], Alison W. Loren[c], Noelle V. Frey[c], David L. Porter[c], Saar I. Gill[c], Elizabeth O. Hexner[c], Selina M. Luger[c], Mary Ellen Martin[c], Shannon R. McCurdy[c], Alexander E. Perl[c], Daria V. Babushok[c] and Keith W. Pratz[c]

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ABSTRACT

Limited treatment options exist for patients with relapsed/refractory (R/R) acute myeloid leukemia (AML). Venetoclax (VEN) in combination with a hypomethylating agent (HMA) or low-dose cytarabine (LDAC) has been recently approved for treatment-naïve patients unfit for intensive induction. Limited data are available to characterize the efficacy of VEN combinations in R/R AML. We retrospectively analyzed 77 patients with a median of 1 prior therapy (range 0–5) treated with VEN combinations for R/R AML or AML secondary to myelodysplastic syndrome (MDS) progressing after HMA monotherapy. The median overall survival (OS) was 13.1 months (95% CI 9.2–15.1). The median progression-free survival (PFS) was 12 months (95% CI 8.2–15.4) with a median duration of response of 8.9 months (95% CI 5.7–13.9). Overall response rate (ORR) was 68% with a composite complete response (CR) and CR with incomplete hematologic recovery (CRi) rate of 53%. VEN combination therapy is efficacious in R/R AML and further prospective studies are warranted.

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KEYWORDS
Relapsed/refractory AML; venetoclax; hypomethylating agent; low-dose cytarabine

Introduction

Relapsed and refractory (R/R) acute myeloid leukemia (AML) is associated with poor outcomes, including a 5-year overall survival (OS) of 12.6% and median OS of 5 months [1]. Treatment options for R/R AML include salvage chemotherapy, targeted therapies, clinical trials, and low-intensity regimens with a hypomethylating agent (HMA) or low-dose cytarabine (LDAC). Venetoclax (VEN) is an oral B-cell lymphoma 2 (BCL-2) inhibitor shown to be effective in *de novo* AML when used in combination with an HMA or LDAC in patients ≥75 years old or those not fit for intensive chemotherapy [2–5].

Several retrospective studies have evaluated the utility of VEN in the R/R setting with composite of complete response (CR) and CR with incomplete hematologic recovery (CRi) rates ranging from a low of 12% to as high as 52% [6–15]. Given the wide range of outcomes, further data are required to determine the utility of VEN in combination with an HMA or LDAC in R/R AML. Herein we present the outcomes of 77 patients with R/R AML treated with VEN in combination with azacitidine (AZA), decitabine (DEC), or LDAC at the Hospital of the University of Pennsylvania, demonstrating excellent overall response rates (ORRs) of 68% with a composite CR and CR with CRi rate of 53%.

Materials and methods

This single-center, retrospective, institutional review board-approved study examined outcomes of patients with R/R AML treated with VEN combinations conducted at the Hospital of the University of Pennsylvania between 1 November 2018 and 31 July 2020. Patients identified by searching the electronic medical record for VEN prescriptions were screened for study inclusion criteria. Patients age 18 years or older who received VEN in combination with either an HMA or LDAC for AML after the failure of at least one line of therapy were included. Patients were also eligible if they had progression to AML from

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myelodysplastic syndrome (MDS) which had been treated with an HMA. Patients were excluded if they had prior treatment with VEN, received VEN with an HMA or LDAC through an interventional clinical trial, concurrently received additional agents in addition to VEN/HMA or LDAC, or if treatment with VEN combination was for maintenance or consolidation.

Concomitant therapy with AZA, DEC, or LDAC was decided at provider discretion. Prior lines of therapy were defined as therapies initiated for active disease and did not include consolidation, maintenance, or allogeneic stem cell transplantation (allo-SCT). All available cytogenetics and next-generation sequencing (NGS) at diagnosis, the time of VEN initiation, and relapse after treatment with VEN were reviewed.

The primary endpoint was OS, defined as survival from VEN initiation until death or last known follow-up. Secondary endpoints included progression-free survival (PFS), duration of response (DoR), ORR, a composite of CR/CRi, and ability to bridge to allo-SCT. Treatment responses and cytogenetic categorization were determined using the European LeukemiaNet (ELN) 2017 criteria [16].

OS, PFS, and DoR were analyzed using the Kaplan–Meier method. Response rates and patient demographic information were assessed with descriptive statistics. Access to directly-identifiable protected health information was limited to the study investigators.

Table 1. Baseline demographics.

Characteristic	$N = 77$
Age – years, median (range)	64 (22–85)
Male – *n* (%)	34 (44)
ECOG performance status – *n* (%)	
0	14 (18)
1	35 (46)
2	13 (17)
3	7 (9)
4	1 (1)
Unknown	7 (9)
Type of AML – *n* (%)	
De-novo	45 (58)
Secondary	18 (23)
Therapy-related	14 (18)
Disease status – *n* (%)	
Relapsed disease	42 (55)
Refractory disease	24 (31)
Post-MDS secondary AML after prior HMA for MDS	11 (14)
ELN genetic risk category – *n* (%)	
Favorable risk	4 (5)
Intermediate risk	17 (22)
Adverse risk	56 (72)
Adverse risk characteristics – *n* (%)	
FLT3-ITD mutation	8 (10)
Complex cytogenetics	15 (26)
TP53 mutation	16 (29)
Prior treatment – *n* (%)	
Median number of prior active lines of therapy received (range)	1 (0–5)
Monotherapy HMA or LDAC	42 (55)
7 + 3	36 (47)
Liposomal daunorubicin and cytarabine	15 (20)
HiDAC	8 (10)
Prior allogeneic stem cell transplant	27 (35)

HMA: hypomethylating agent; MDS: myelodysplastic syndrome; ELN: European LeukemiaNet; LDAC: low dose cytarabine; 7 + 3: daunorubicin and cytarabine; HiDAC: high dose cytarabine

Results

We identified 99 patients with R/R AML treated with VEN in combination with either an HMA or LDAC over the study period. Twenty-two patients were excluded for incomplete medical records or receiving care primarily at other institutions ($n = 14$), therapy as consolidation or maintenance ($n = 7$), or receiving prior treatment with VEN ($n = 1$) (Table 1). The median age was 64 years (IQR 54–69) and 44% were male. Fifty-five percent had relapsed AML, 31% were primary refractory, and 14% had transformed AML after failure of an HMA for MDS. Of 77 patients, 60 (78%) received VEN in combination with AZA, 13 (17%) in combination with DEC, and 4 (5%) received VEN in combination with LDAC. Patients were treated for a median of 2.8 months (IQR 1.8–5.8) and 97% ($n = 75$) required a dose adjustment. The most common reasons for dose adjustment included drug interactions ($n = 61$), adjustment for cytopenias with subsequent cycles after achieving initial response ($n = 30$), or non-hematologic toxicities ($n = 10$). The choice of combination agent and dose adjustment of VEN was performed at treating physicians' discretion, with VEN regimens summarized in Supplemental Tables 1 and 2.

After a median follow-up of 9.9 months (95% CI 0.4–26.8), 38% ($n = 29$) of patients were alive (Figure 1), with a median OS of 13.1 months (95% CI 9.2–15.1). ORR was 68% with a composite CR/CRi rate of 53% (Table 2). Response rates could not be assessed in seven patients who died or were transitioned to hospice without a repeat bone marrow biopsy; for the study, these patients were considered non-responders. The median time to response was 1 month (95% CI 0.8–1.8). Median PFS was 12 months (95% CI 8.2–15.4, Figure 2) with a median DoR of 8.9 months (95% CI 5.7–13.9 months).

Table 3 outlines the OS in various subgroups. Patients with prior HMA or LDAC had a median OS of 9.2 months (95% CI 6.8–11.7). Patients with post-MDS secondary AML arising after the failure of an HMA ($n = 11$) had a median OS of 3.5 months (95% CI 0.6-not reached). Patients with primary refractory disease ($n = 24$) had a median OS of 11.8 months (95% CI 7.1–18) compared to 14.7 months (95% CI 9.2–18) in those with relapsed disease ($n = 43$). In responders (ORR 68%, $n = 52$), the median OS was 15.1 months (95% CI 10.7–19.8).

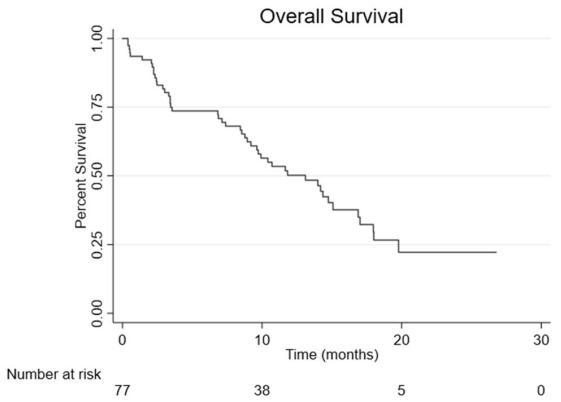

Figure 1. Overall survival. Kaplan–Meier curve of OS for the entire cohort. The median OS was 13.1 months (95% CI 9.2–15.1).

Table 2. Outcomes to venetoclax combinations.

Best response to venetoclax – *n* (%)	*N* = 77
Complete response (CR)	27 (35)
Complete response with incomplete hematologic recovery (CRi)	14 (18)
Composite CR (CR and CRi)	41 (53)
Partial response	11 (14)
Progression	25 (32)
Overall response rate	52 (68)
Time to best response, months – Median (95% CI)	1.0 (0.8–1.8)

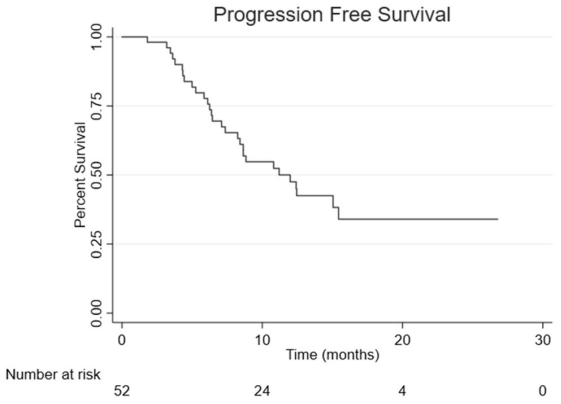

Figure 2. Progression-free survival. Kaplan–Meier curve of PFS for the entire cohort. The median PFS was 12 months (95% CI 8.2–15.4)

Seventeen patients were treated with VEN combinations as a bridge to an allo-SCT and 6 patients with R/R AML following allo-SCT were bridged to donor lymphocyte infusion (DLI). These patients had an ORR of 76% and a composite of CR/CRi of 71% to VEN combination therapy. Four patients without a response to VEN received other therapies, including investigational chimeric antigen receptor T-cell therapy ($n = 2$), were switched from AZA with VEN to DEC with VEN ($n = 1$), or received salvage chemotherapy with mitoxantrone, etoposide and cytarabine (MEC) to induce remission before allo-SCT ($n = 1$). Patients bridged to allo-SCT had a median OS of 19.8 months (95% CI 14.2-not reached) and PFS was not reached (95% CI 6.4-not reached).

Twenty-seven patients were treated with VEN combinations after relapsing from an allo-SCT. These patients had a median age of 60 years (range 25–75) and had failed a median of two prior therapies (range 0–5). VEN treatment continued for a median of 2.8 months, with one patient continuing treatment at the data cutoff. The ORR was 67%, 13 patients (48%) had CR, and 2 (7%) had CRi. Ten patients were bridged to subsequent allo-SCT and 6 patients went on to receive DLI. The median OS was 14.7 months (95% CI 7.4–18, Figure 3), and the median PFS was 12.4 months (95% CI 7.4-not reached, Figure 3).

Sixty patients relapsed following VEN combination therapy and went on to receive subsequent salvage therapies (detailed in Supplemental Table 3), which included retreatment with VEN and an HMA or LDAC ($n = 12$) and HMA or LDAC monotherapy ($n = 7$).

Fifty patients had NGS done at the time of VEN initiation. The most common mutations are outlined in Figure 4. Of the 61 patients with NGS data at AML diagnosis, the most common mutations were DNMT3A (28%), TP53 (20%), TET2 (16%), and ASXL1 (16%). Twenty patients (26%) had a change in their mutation status between diagnosis and initiation of VEN; NGS data were not evaluable for 27 (35%) of patients. Some patients ($n = 27$) did not have repeat NGS data available if they had primary refractory AML or had an insufficient sample sent prior to initiation of VEN. Of the 30 patients who relapsed after VEN treatment, 20 (67%) had NGS data available; of these 11 (55%) had changes in their mutational status at the time of relapse. The most common mutations present at relapse after VEN therapy were DNMT3A (40%), TP53 (60%), TET2 (30%) and SRSF2 (25%) with 6 (30%) having two or more new mutations.

Discussion

In this retrospective study of VEN combination therapies in the R/R setting, we found clinically favorable response rates and survival, with a median OS of 13.1 months, compared to historical outcomes. Our results showed particular benefits in patients bridged to an allo-SCT, with a median OS was 19.8 months (95% CI 14.2-not reached), and in patients relapsing after allo-SCT, with a median OS of 14.7 months (95% CI 7.4–18). Our data support the efficacy of VEN combinations in patients with R/R AML.

Our cohort had a higher ORR of 68% and composite of CR/CRi of 53% compared to 19–64% and 12–52%, respectively, in historical studies [6–15]. One possible explanation could be the more frequent combination

Table 3. Overall survival in select subgroups.

Subgroup	Median OS – months (95% CI)
Survival based on prior therapies	
Daunorubicin and cytarabine induction or high dose cytarabine, $n=46$	14.7 (11.8–18)
Liposomal daunorubicin and cytarabine, $n=16$	8.8 (3.5–15)
HMA or LDAC monotherapy, $n=42$	9.2 (6.8–11.7)
AML after HMA for MDS, $n=11$	3.5 (0.6-not reached)
Survival based on relapsed or refractory disease	
Relapsed, $n=43$	14.7 (9.2–18)
Refractory, $n=24$	11.8 (7.1–18)
Survival based on concomitant agent	
Azacitidine, $n=60$	14.4 (10.4–18)
Decitabine, $n=13$	7.4 (1.4–13.1)
LDAC, $n=4$	3.3 (3.3-not reached)
Survival based on allogeneic stem cell transplant	
Prior allogeneic stem cell transplant	14.7 (7.4–18)
Subsequent allogeneic stem cell transplant	19.8 (14.2-not reached)
Survival based on response to VEN treatment	
CR/CRi, $n=41$	18 (14.7-not reached)
All responders, $n=52$	15.1 (10.7–19.8)

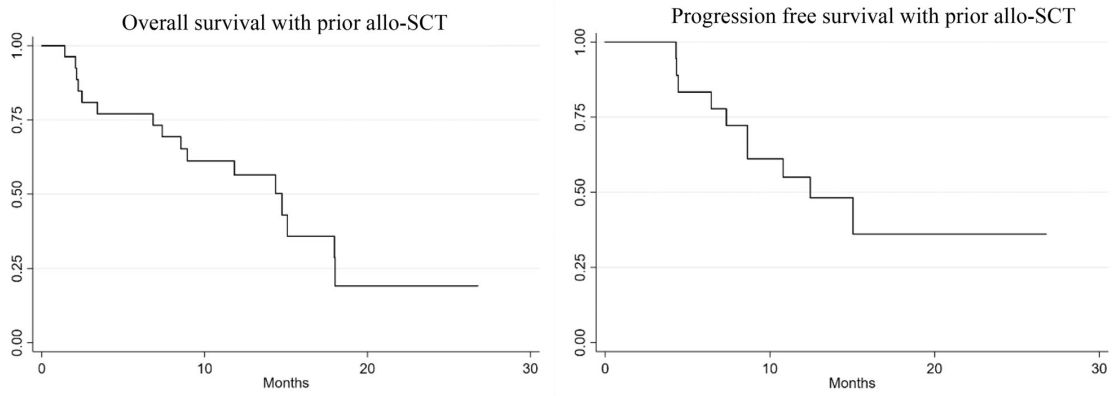

Figure 3. Survival after relapse from allo-SCT. Kaplan–Meier curve of OS and PFS for the 27 patients who relapsed after allo-SCT. The median OS was 14.7 months (95% CI 7.4–18) the median PFS was 12.4 months (95% CI 7.4-not reached)

with AZA in our study, as prior reports showed improved outcomes in patients with AZA + VEN compared to DEC or LDAC + VEN [10]. Future studies are needed to confirm this finding, as our study was retrospective, had few patients in the DEC and LDAC groups, with potential for confounding due to treatments chosen by patient treatment teams.

Our data also suggest significant benefits in patients that can be bridged to an allo-SCT, sparing the toxicities associated with intensive conventional chemotherapy historically used to induce remissions in R/R patients. These outcomes are consistent with prior reports of allo-SCT following treatment with VEN + HMA [17,18]. We additionally observed significant benefits of VEN used for treatment of relapse after allo-SCT. In our study, 27 patients were treated with VEN combinations after relapsing after allo-SCT. These patients had an ORR of 67%, composite of CR/CRi of 56% and median OS of 14.7 months (95% CI 7.4–18). Six patients were able to be bridged to DLI, with five still alive at the time of data collection. This compares favorably to outcomes of AZA alone with or without DLI, where ORR was 30% and a median OS of 3.9 months [19]. While further confirmation is needed, it appears that VEN combinations may have utility in patients who relapse post- allo-SCT.

As outlined by Stahl et al., molecular markers including NGS mutations can predict response to VEN therapy, with TP53, KRAS/NRAS, and SF3B1 mutations associated with worse OS [10]. However, given the small sample sizes of patients with each mutation, it is difficult to draw firm conclusions regarding outcomes based on mutational status at the time of VEN initiation. Another interesting analysis is the emergence of mutations at the time of disease relapse. Stahl et al. reported that five out of ten patients with available NGS information at the time of relapse had a new emergent mutation and a more complex molecular profile. Similarly, we found that of the 20 patients with available NGS data in our study, 11 (55%) had a new mutation at relapse, including gains of WT1, DNMT3A, FLT3, TP53, CEBPA, TET2, ETV6, and SMC1A. While the development of new

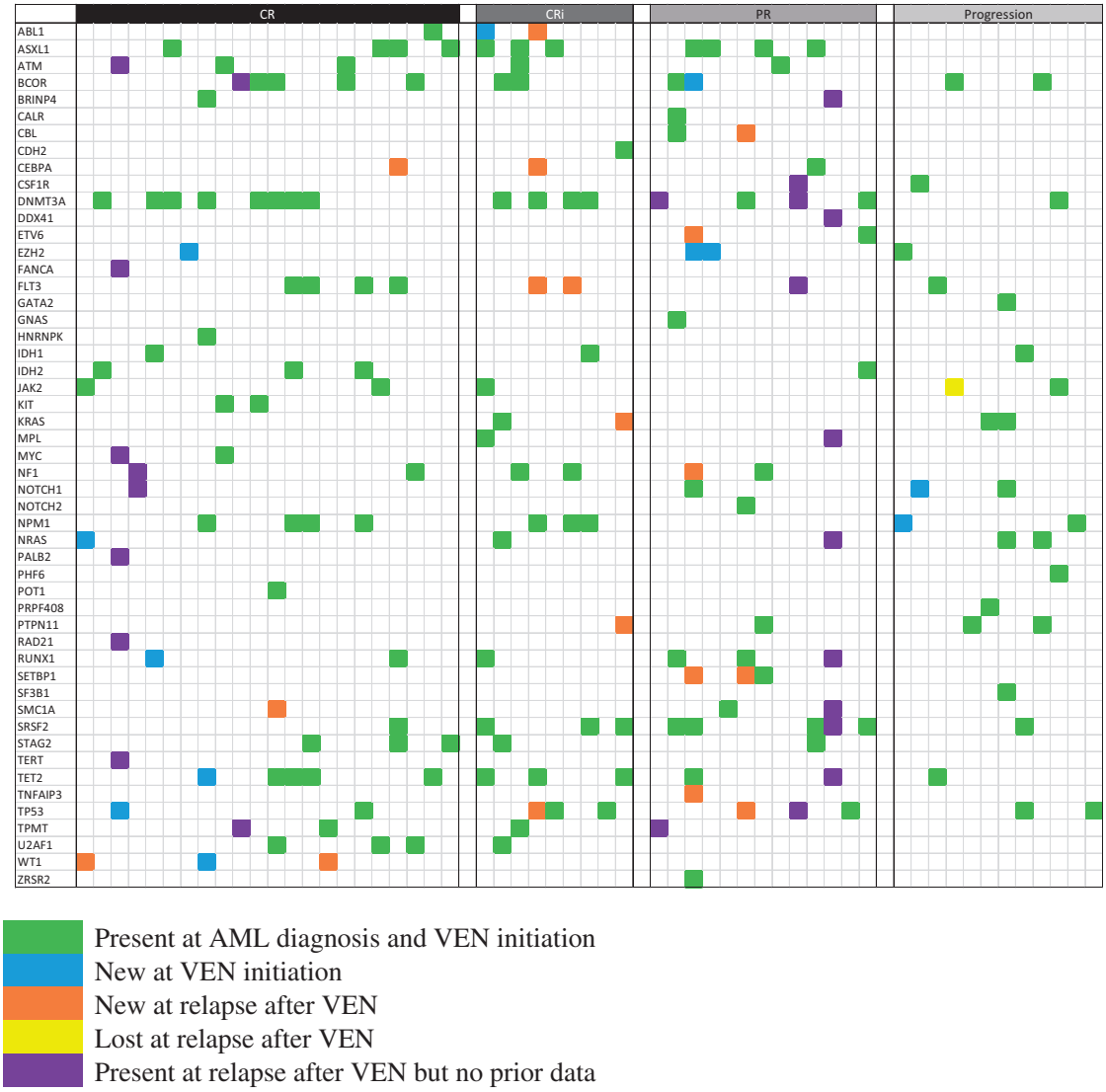

Figure 4. NGS data. Next generation sequencing data for patients correlated to response rates. Vertical columns represent individual patients' mutations.

mutations is consistent with the known pathogenesis of AML with relapses occurring to the development of new mutations, further data are needed to define how this information can help guide our practice and potentially explain mechanisms of resistance.

The limitations of this retrospective analysis include that the choice of combination therapy and dose adjustments were determined by a treating physician and toxicity data could not be reliably collected. In addition, patients who died prior to their first disease assessment or transitioned to hospice were included as non-responders while they were excluded from consideration in previous reports [7,8,11,15].

This study highlights that VEN combination regimens have significant activity in the treatment of patients with R/R AML, including as a bridge to allogeneic SCT and for relapse after allogeneic SCT. We found that the combination of VEN with LDAC or an HMA has clinically meaningful activity with a composite of CR/CRi of 53% and median OS of 13.1 months (95% CI 14.2-not reached) which extends to 19.8 months (95% CI 14.2-not reached) in those able to be bridged to allo-SCT. Future randomized prospective studies would help to define response rates in individual populations.

Disclosure statement

The authors report there are no competing interests to declare.

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