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CASE REPORT

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Real-life experience of venetoclax and hypomethylating agents in acute myeloid leukemia patients not candidates for intensive chemotherapy or who are refractory/relapsed: A single-centre experience

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Abstract

We report our experience with venetoclax/hypomethylating agents (Ven/HMA) in 8 AML patients not candidates for intensive CT or refractory/relapsed with limited treatment options. The response rate was 50%. Venetoclax was well-tolerated in 62.5% of the patients. Ven/HMA provides a benefit particularly when used in patients without prior HMA exposure.

KEYWORDS

acute myeloid, elderly, hypomethylating agents, leukemia, Venetoclax

1 | INTRODUCTION

Acute myeloid leukemia (AML) is the most common acute leukemia in the adult population and largely affects older patients with a median age at diagnosis of 68 years.[1] Elderly patients with AML often respond poorly to induction chemotherapy as a result of higher frequency of adverse genome features and increased resistance to treatment.[2,3] Furthermore, because of comorbidities, compromised organ function, and poor performance status, older patients may not be candidates for conventional cytotoxic induction therapies,[2,4–6] and therefore, treatment options for unfit patients have historically been limited.[7] Less intensive approaches to treatment, such as low-dose cytarabine (LDAC), have shown poor response rates (11%–19%) and short median survival rates (<6 months).[8,9] Similarly, hypomethylating agents (HMA) azacitidine and decitabine in monotherapy are associated with a tolerable safety profile, complete remission (CR) plus CR with incomplete count recovery (CRi) rates of 15%–30%, and median overall survival (OS) of <12 months.[10,11] In November 2018, the Food and Drug Administration (FDA) approved the selective BCL-2 inhibitor venetoclax in combination with either HMA or LDAC in older or unfit patients with AML.[7]

Venetoclax has shown encouraging activity when combined with HMA agents.[2,12] Venetoclax 400 mg plus HMA (Ven/HMA) in newly diagnosed AML patients without prior HMA exposure led to a 73% rate of CR + CRi,[2] while, in relapsed/refractory (r/r) AML patients (61% with prior HMA failure), it was observed with an ORR (CR + CRi) of 51%.[12] The combination is well-tolerated even in fragile

patients and is associated with low treatment-related mortality.[2] These promising data, as well as availability of the drug, have led to significant off-label use of the combination Ven/HMA in both the frontline and the relapse/refractory setting, where it also has significant activity.[13,14] We aimed to explore Ven/HMA treatment in AML patients not candidates for intensive chemotherapy or who are refractory/relapsed in daily clinical practice.

2 | METHODS

We conducted a retrospective and descriptive analysis of real-world data from AML patients treated with the combination of venetoclax with HMA at Infanta Sofia University Hospital from April 2019 to January 2020. Data were collected using a query to already available secondary data (electronic clinical records), not requiring specific IRB approval. Written informed consent was obtained for the publication of data from patients still alive or from relatives in the case of deceased patients.

Demographic and clinical data were obtained from the electronic medical record (Selene®). Treatment data were collected from the electronic prescription module (Farmatools®). Patients received at least one cycle of treatment: 4 weeks of 400 mg oral venetoclax daily/HMA (either decitabine 20 mg/m2 for 5 days or 5-azacytidine for 7 days).

Venetoclax is a cytochrome p450 (CYP3A) substrate; therefore, if strong CYP3A inhibitors such as antifungal drugs (posaconazole, isavuconazole) were required, the venetoclax dose was reduced. Samples from the bone marrow aspirate were collected before starting venetoclax/HMA treatment and later for the evaluation of treatment response. For blast count, conventional cytology and immunophenotyping by flow cytometry were performed. Cytogenetic analysis included standard cytogenetic and fluorescence in situ hybridization (FISH) assessments. PCR for molecular analysis of MLL, FLT3, NMP1, and CEBPA gene were performed in most of the patients. In addition, a myeloid next-generation sequencing (NSG) panel was used. Cytogenetic risk was assessed according to 2017 European LeukemiaNet (ELN) recommendations for genetic risk stratification.[15] Response to treatment was defined as either complete remission (CR) or CR with incomplete blood count recovery (CRi) according to the International Working Group.[16–18]

TABLE 1 Demographics and Clinical Characteristics

Characteristics	Patients $N = 8$
Age, years; median (range)	74.5 (46–77)
≥65 yrs, *n* (%)	7/8 (87.5)
Sex, *n* (%)	
Women	5/8 (62.5)
Performance status (ECOG), *n* (%)	
0	5/8 (62.5)
1	1/8 (12.5)
2	2/8 (25.0)
Diagnosis, *n* (%)	
AML de novo	1/8 (12.5)
AML Secondary	7/8 (87.5)
MDS-EB2	4/8 (50.0)
MDS-EB1	1/8 (12.5)
CMML	2/8 (25.0)
Prior HMA treatment, *n* (%)	
Yes	6/8 (75.0)
Blast at diagnosis, *n* (%)	
<30%	2/8 (25.0)
30%–50%	3/8 (37.5)
>50%	3/8 (37.5)
Cytogenetic, *n* (%)[a]	
Complex	2/8 (25)
ELN cytogenetic risk[b]	
Adverse	4/8 (50%)
Intermediate	4/8 (50%)
Main gene mutations, *n* (%)	
TET2	3/8 (37.5)
IDH2	3/8 (37.5)
ASXL1	2/8 (25.0)
NRAS	2/8 (25.0)
RUNX1	1/8 (12.5)
CEBPA	1/8 (12.5)
JAK2	1/8 (12.5)

Abbreviations: AML, acute myeloid leukemia; ASXL1, ASXL transcriptional regulator 1; CEBPA, CCAAT enhancer binding protein alpha; CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agents; IDH2, isocitrate dehydrogenase (NADP[+]) 2; JAK2, Janus kinase 2; MDS-EB, myelodysplastic syndrome with excess blast type 1 or 2; NRAS, neuroblastoma RAS viral oncogene homolog; RUNX1, RUNX family transcription factor 1; TET2, Tet methylcytosine dioxygenase 2.

[a]In one patient, metaphases did not grow.

[b]2017 European LeukemiaNet (ELN) recommendations for genetic risk stratification.

3 | RESULTS

We identified 8 patients diagnosed with AML who received combined therapy with venetoclax and HMA. Table 1 summarizes the demographics and clinical characteristics of patients. The median age was 74.5 years, most of them (7/8) were older than 65 years and 5/8 (62.5%)

were women. Seven (87.5%) patients presented a secondary AML, mostly to myelodysplastic syndrome with excess blast type 2 (MDS-EB2) (Table 1). Two of 7 patients (26.8%) had a complex cytogenetic profile. Of note in molecular analysis are the following gene mutations: 3/8 (37.5%) TET2, 3/8 (37.5%) IDH2, 2/8 (25.0%) AXL1, 2/8 (25.0%) NRAS, 1/8 (12.5%) RUNX1, 1/8 (12.5%) CEBPA, and 1/8 (12.5%) JAK2. No patients harbored mutations in MLL, FLT3, or NMP1 genes. Additional gene mutations are provided in Table 2. Patients presented an adverse (50%) or intermediate (50%) cytogenetic risk (Table 2).

The majority of patients (75%) had had prior HMA (azacytidine) exposure as a treatment for a previous MDS. Ven/HMA was the first-line treatment for AML in 5/8 (62.5%) of the cases, and decitabine was the most frequent HMA used (75%). The median treatment duration was 92 days (24–572). Five patients (62.5%) received 1–3 cycles of therapy (Table 2).

Two patients received venetoclax at a dose of 400 mg. Lower venetoclax doses were administered in 6/8 patients because of concomitant use of antifungals; thus, 5/8 patients receiving Posaconazole were treated with venetoclax 70 mg (venetoclax dose was increased to 400 mg after withdrawal of Posaconazole in two of them) and one case on Isavuconazole therapy received venetoclax 100 mg.

The treatment response rate (CR/CRi) was 50%. Among the four responders, 2 presented adverse cytogenetic risk, 2 did not have prior HMA exposure, and 3 received Ven/HMA as their first-line treatment for AML (Table 2). Two responders maintained the response over 19 and 18 cycles. One of them was still on therapy at the time of analysis (18 cycles).

Venetoclax was well-tolerated in 5/8 (62.5%) of patients. Cytopenia was the most frequent toxicity: neutropenia (any grade) occurred in all patients (100%) and thrombocytopenia in 1/8 (12.5%).

Treatment discontinuation or decrease in the duration of treatment (2 weeks on 2 weeks off schedule) was reported in three patients due to neutropenia; 2 patients presented disease progression during the period without treatment. Two deaths occurred from infections; one of them due to bilateral pneumonia without microbriological identification, and another due to fungal pneumonia.

Table 2 summarizes the clinical characteristics, treatment, and response of patients in our case series.

3.1 | Patient 1

A 74-year-old woman presented with AML secondary to a chronic myelomonocytic leukemia (CMML). At diagnosis, in bone marrow, aspirate presented 23% and 18.5% of blast according to cytomorphology and high-flow cytometry (IF), respectively. Genetic analysis showed karyotype 47, XX,+21, NPM1-, FLT3-y CEBPA- by FISH and mutations in ASXL1 and TET2 genes by NSG using a myeloid panel. She did not receive any prior treatment, and venetoclax/decitabine was her first-line treatment. She had not been previously treated with HMA. After 5th cycle showed by bone marrow evaluation a CR. The main adverse event during the treatment was neutropenia. She received 19 cycles, with the latter being incomplete. Treatment was discontinued due to SARS-CoV-2–negative bilateral pneumonia from which she died.

3.2 | Patient 2

A 77-year-old woman was diagnosed with de novo AML. She presented 45% and 34.8% of blasts by conventional cytology or IF, respectively, before starting first-line treatment with venetoclax plus decitabine (Ven/Dec). She had a normal karyotype without abnormal gene variants. Her cytogenetic risk was intermediate. Bone marrow evaluation on the 28th day of the second cycle showed a CR, and the percentage of blast morphology cells decreased up to less than 3% and 0.65% by IF. The patient achieved a complete response. She has received 18 Ven/Dec cycles and continues on treatment at the time of analysis. Due to neutropenia, venetoclax treatment duration was decreased (400 mg 2 weeks on 2 weeks off schedule) from the third cycle onwards.

3.3 | Patient 3

A 75-year-old woman was diagnosed with AML secondary to a MDS with excess blast type 2 (MDS-EB2) who had received previous treatment lines with decitabine and also with Vyxeos Liposomal® (daunorubicin/cytarabine). Analyses of peripheral blood revealed the presence of 30% blasts by CC and 48% blats by IF. Cytogenetics revealed 18 metaphases with karyotype 46,XX.t(1;3)(p36;q21)del (5)(q22q35) and 2 metaphases with 46,XX,t(1;3)(p36;q21). Sequencing analyses reveled mutations in WT-1 and SETBP1 genes. Venetoclax plus decitabine was administered as a second-line treatment for the AML. Blood smear evaluation at the start of third cycle revealed 48% of blast morphology cells, confirming disease progression.

3.4 | Patient 4

A 46-year-old man presented with AML secondary to MDS-EB2 who had previously received intensive chemotherapy with 2 cycles of idarubicin plus cytarabine (3 × 7)

TABLE 2 Characteristics of patients in case series

Patient	Age	AML type	Cytogenetic risk	Cytogenetic	PCR (MLL/FLT3/NPM1/CEBPA) and NGS	AML treatment line	Prior HMA	HMA/Ven treatment	Response
1	74	Second CMML	Adverse	47, XX + 21	ASXL1, TET2	First	NO	Aza/Ven 19 cycles	CR
2	77	De novo	Intermediate	Normal karyotypes	None	First	NO	Dec/Ven 18 cycles[a]	CR
3	75	Second MDS EB2	Adverse	46,XX.t(1;3)(p36;q21)del (5)(q22q35)[18 metaphases] /46,XX,t(1;3)(p36;q21)[2 metaphases].	WT1, SETBP1	Second	YES	Dec/Ven 3 cycles	DP
4	46	2nd MDS EB2	Intermediate	46, XY.t(3;13). Monosomy cr7.	JAK2, SF3B1	Second	YES	Dec/Ven 2 cycles	DP
5	77	Second MDS EB1	Intermediate	NA[b]	IDH2, NRAS, SRSF2, TET2, STAG2	First	YES	Dec/Ven 2 cycles	DP
6	74	Second MDS EB2	Adverse	normal karyotype	ASXL1	First	YES	Dec/Ven 1 cycles	PR
7	71	Second MDS EB2	Intermediate	47, XY +8	IDH2, NRAS, NF1, STAG2	First	YES	Dec/Ven 2 cycles	CRi
8	77	Second CMML	Adverse	normal karyotype	EZH2, IDH2, RUNX1, TET2, CEBPA	Third	YES	Aza/Ven 7 cycles	CR

[a]Currently on treatment.

[b]Metaphases did not grow.

Abbreviations: AML, acute myeloid leukemia; ASXL1, ASXL transcriptional regulator 1; Aza, azacytidine; CEBPA, CCAAT enhancer binding protein alpha; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete count recovery; DP, disease progression; Dec, decitabine; EZH2, enhancer of Zeste 2 polycomb repressive complex 2 subunit; FLT3, Fms-related receptor tyrosine kinase 3; HMA, hypomethylating agents; IDH2, isocitrate dehydrogenase (NADP[+]) 2; JAK2, Janus kinase 2; MDS-EB, myelodysplastic syndrome with excess blast type 1 or 2; MLL1, mixed-lineage leukemia 1; NPM1, nucleophosmin 1; NRAS, neuroblastoma RAS viral oncogene homolog; NA, not available; NF, neurofibromin 1; NGS, next-generation sequencing; PCR, polymerase chain reaction; RUNX1, RUNX family transcription factor 1; SETBP1, SET binding protein 1; SF3b1, splicing factor 3B subunit 1; SRSF2, serine and arginine rich splicing factor 2; STAG2, stromal antigen 2; TET2, Tet methylcytosine dioxygenase 2, Ven, venetoclax; W1, WT1 transcription factor.

that had been refractory. The patient also had previously received azacitidine as a treatment for MDS-EB2. Bone marrow evaluation showed basal blasts by IF of 38.6%. An anormal karyotype was observed (46,XY,t[3;13], monosomy of cr7) and harbored mutations in JAK2 and SF3B1 genes by NSG. Venetoclax combined with decitabine was administered as a second-line treatment for AML. Analyses of peripheral blood revealed in revaluation on the 28th day of the first cycle of treatment a blast morphology of 60.46%, indicating disease progression.

3.5 | Patient 5

A 77-year-old woman presented with a diagnosis of AML secondary to MDS-EB1 who had received a previous treatment with azacytidine. Bone marrow analysis showed 55% of blast morphology cells by conventional cytology and an 50% of blast cells (including promonocytes) according to immunophenotyping. Karyotype analysis could not be performed because metaphases did not grow. Mutations in IDH2, NRAS, TET2, and STATG2 were detected by NSG. AML was treated with venetoclax plus decitabine as a first-line treatment. Analyses of peripheral blood revealed clinical progression in the revaluation on the 17th day of the second cycle of treatment, with leukocytosis and gingival hypertrophy and 12% of blast morphology cells.

3.6 | Patient 6

A 74-year-old woman was diagnosed with AML secondary to MDS-EB2, for which she had received a previous treatment with azacytidine. Analysis of bone marrow aspiration presented 40% of blast morphology cells and 26% blast cells evaluated with immunophenotyping. The patient had a normal karyotype, and mutations were only detected in ASXL1 using NGS. She achieved a partial response with venetoclax plus decitabine as a first-line treatment for her AML. Revaluation of bone marrow samples on the 8th day of the second cycle of treatment revealed a percentage of IF of blast of 8%. She received 24 days of Ven/Dec. She suffered from neutropenia and died due to a fungal pneumonia.

3.7 | Patient 7

A 71-year-old man presented with AML secondary to MDS EB2, for which he had received a previous treatment with azacytidine. Before starting venetoclax plus decitabine treatment, bone marrow assessment showed 50% and 43% of blasts by conventional cytology or IF, respectively. The patient's karyotype was 47,XY,+8. Mutations were detected in IDH2, NRAS, NF1, and STAG2 genes. He was treated with venetoclax plus decitabine as a first-line treatment. In bone marrow revaluation on the 8th day of the second cycle of treatment, the IF blast percentage decreased to 0.1% showing a complete response. He received 2 cycles of Ven/Dec as a first-line AML treatment. The second one was stopped due to neutropenia, and subsequently, disease progression occurred.

3.8 | Patient 8

A 77-year-old man presented with AML secondary to CMML, for which he had received a previous treatment with induction chemotherapy (3×7) and cytarabine at high doses. He also had received azacytidine for CMML. Bone marrow analysis showed 45% of blast morphology cells with a normal karyotype. Sequencing analyses revealed mutations in EZH2, IDH2, RUNX1, TET2, and CEBPA genes. Venetoclax plus azacytidine was prescribed as a third-line treatment for his AML. Bone marrow analysis at 30th day of the second cycle of treatment showed blast morphology and the blast percentages according to immunophenotyping had decreased to 0%, thus, reaching a complete response. The patient achieved transfusion independence. After 7 cycles, treatment was discontinued due to neutropenia, and subsequently, DP occurred (25% blasts in peripheral blood).

4 | DISCUSSION

Herein, we report our single-centre experience with venetoclax in combination with HMA for the treatment of patients with AML in daily clinical practice. Five patients were not candidates for intensive chemotherapy, and the study treatment constituted their first therapeutic line for AML. Two of them had not previously received treatment with HMA. There were three refractory/relapsed AML patients to prior therapeutic lines for AML.

In this series of patients, a response rate (CR/CRi) of 50% was observed. In consonance with data reported in previous studies, [8,19] herein, a better and more sustained response over time (19–18 cycles) was achieved in those patients who had not previously received treatment with HMA, and the Ven/HMA treatment constituted their first therapeutic line for AML. Therefore, our results reflect a greater benefit of Ven/HMA combination in patients who received it in accordance to the licensed indication. As was observed by other authors, [2] the AML origin (de novo or secondary to other myelodysplastic syndrome) seems not to affect to response of treatment.

The results of Ven/HMA combination for AML treatment are impressive in the frontline setting. In a phase Ib/II trial, the reported response rate was of 54% (CR/CRi), which increased up to 62% among patients without HMA prior exposure. [8] DiNardo showed a response rate of 73% (CR + CRi) in a 400 mg cohort of an open-label dose escalation trial, where prior treatment with HMA was an exclusion criterion. [2] In our cohort, 5 patients received Ven/HMA as a first-line treatment, of whom 3, with prior HMA exposure, did not achieve complete remission, while 2 patients who did not receive prior HMA achieved CR and it was maintained for 18–19 cycles.

Published data in the refractory/relapse AML in real-life settings are not homogeneous. In a retrospective study with 43 patients [median age 68 years; 77% of them previously treated with HMA; 83% receiving Ven/HMA combinations for R/R myeloid malignancies (91% AML)], DiNardo et al. observed an overall response rate (ORR) of 21% [5% CR, 7% CRi, 9% morphological leukemia-free state (MLFS)]. [14] By contrast, Aldoss et al. reported an ORR of 64% (30% CR, 21% Cri, and 12% MLFS) in a retrospective analysis of 33 adults (median age 62 years) with R/R AML, 61% of them with prior HMA exposure. [12]

In our series of patients, 2 of 3 refractory/relapsed patients did not achieve response. In this sense, off-label use of the combination should not be encouraged due to a low probability of response and poor median survival. Recently, an investigation with R/R AML patients within the PETHEMA registry delivered similar or even poorer results of venetoclax-salvage treatment, with marginal probabilities of CR/CRi (12.4%) and poor overall survival (median: 104 days; 95% CI: 56–151).[20] Specifically, it is noteworthy that in our study a refractory old (77 years) patient with prior azacytidine exposure, who received Ven/Aza as a third-line treatment for his secondary AML, achieved CR (maintained over 7 cycles) and transfusion independence. This patient had adverse cytogenetic risk harboring mutations in IDH2 and RUNX1genes among others. One pattern of primary resistance to venetoclax comprised RUNX1.[7] The significance of RUNX mutated as a driver of treatment resistance remains uncertain,[7,14] as RUNX1-mutated cases were present among frontline patients with long remission[7] and in R/R AML respondents.[14] It should also be noted that all frontline patients harbored either a co-occurring IDH or SRSF2 mutation.[7]

Treatment response was not achieved in four of our eight patients. These patients with intermediate/adverse cytogenetic risk presented different gene mutations including the kinases JAK2 and NRAS, related to primary resistance to venetoclax.[7]

A recent study showed patients to have morphologically refractory disease based on the assessment of total blast count alone. Interval molecular profiling before and after only one cycle of therapy revealed a surprising degree of intratumoral clonal heterogeneity not evident from examination of bulk blast level alone.[7] These findings highlight the potential for rapid, polyclonal, and divergent changes in clonal architecture, even in patients with "no morphologic response."[7]

As expected, and in consonance with published data,[8,13,14] the most frequent toxicity observed in our real-life cohort was cytopenia. As reported in other observational studies,[14] herein, neutropenia occurred in all patients receiving Ven/HMA therapy. Strict adherence to a 4 weeks schedule of Ven 400 mg/HMA (either decitabine 20 mg/m2 for 5 days or 5-azacytidine for 7 days with Ven daily) results in serious therapy-related neutropenia within a few cycles.[13]

Mitigation of severe neutropenia in patients who have achieved a response is a major challenge with the Ven/HMA treatment combination and requires significant modifications of therapy over time.[13] In our series, it was necessary to decrease the duration of venetoclax to 2 weeks on and 2 weeks off due to neutropenia in one responder, who continues on treatment at the time of analysis. Two other patients who achieved response, however, discontinued treatment due to neutropenia or infection. Subsequently, they both presented DP.

Several authors[13] recommend administering Granulocyte-macrophage colony-stimulating factor (GM-CSF) as the initial approach to severe neutropenia and, in patients in CR, to decrease the duration of venetoclax considering treatment schedules that include week-break. If neutropenia still remains, it is recommended a 50% dose reduction of the HMA provided the bone marrow is hypocellular with no evidence of leukemia.[13] These recommendations would not apply to patients who remain with persistent neutropenia because of a significant burden of active disease. They should continue to be treated at full dose intensity until achieving CR or at least until there is a low burden of disease. [13]

5 | CONCLUSION

Our real-life data show that treatment with the combination Ven/HMA for AML patients not candidates for intensive chemotherapy or are refractory/relapsed is a therapeutic option, with an acceptable safety profile, that provides benefits particularly in patients who received it as a first-line AML treatment and had no prior HMA

exposure. Therefore, Ven/HMA could play a significant role in current clinical practice for patients not candidates for intensive chemotherapy.

AUTHORS CONTRIBUTION

AR and RH conceived the research. AR, EG, JAV, MJP, ASV, CNTS, and RH contributed to patient identification and data acquisition. AR participated in the manuscript conceptualization and drafting. All authors read and approved the final manuscript.

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CONFLICTS OF INTERESTS

The authors declare that they do not have any conflict of interest as a consequence of this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Not applicable to this article as it is a retrospective description of the cases after written consent for publication has been provided for all patients.

CONSENT

Written consent for the case publication was provided for all patients.

MATERIAL FROM OTHER SOURCES

In this article, we do not reproduce any material from other sources.

CLINICAL TRIAL REGISTRATION

Not applicable – we present a case series.

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