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Venetoclax combination therapy with hypomethylating agents in young adults with relapsed/refractory acute myeloid leukaemia

Nerea Báez-Gutiérrez, Héctor Rodríguez-Ramallo, María Antonia-Pérez Moreno, Eduardo-Rodriguez Arboli* and Laila Abdel-kader Martín*

***Abstract*:** In recent years, one of the most successful advances in treating acute myeloid leukaemia (AML) has been the combination of the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax with hypomethylating agents (decitabine or azacytidine). This combination treatment has an accelerated approval by the Food and Drug Administration for newly diagnosed AML adults who are 75 years of age or older or who have comorbidities and are not eligible to receive intensive induction chemotherapy. AML is the most common form of acute leukaemia in adults, with a median age at diagnosis of 68 years. Consequently, most of the patients included in the studies are elderly. Traditionally, young patients achieve higher remission rates compared with the elderly AML population. Although venetoclax combination therapy could become a treatment option for treating young patients with relapsed/refractory AML, this regimen has not been systematically tested in this setting. In this study, we summarize the currently available evidence on the treatment of venetoclax in combination with hypomethylating agents for the treatment of young relapsed/refractory AML patients, in addition to our experience in clinical practice with two case reports. Venetoclax, combined with hypomethylating agents, seems to be an effective option for young relapsed/refractory AML patients. However, due to the poor quality of the evidence, additional well-designed studies with greater numbers of patients are needed to confirm the effectiveness and safety of venetoclax combination regimens for this population.

Keywords: acute myeloid leukaemia, hypomethylating agent, refractory, relapsed, venetoclax, young patients

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Correspondence to:
Héctor Rodríguez-Ramallo
Hospital Pharmacy Department, Virgen del Rocio University Hospital, Avda. Manuel Siurot s/n, 41013 Seville, Spain.
hectorodra@gmail.com

Nerea Báez-Gutiérrez
María Antonia Pérez-Moreno
Laila Abdel-kader Martín
Hospital Pharmacy Department, Virgen del Rocio University Hospital, Seville, Spain

Eduardo Rodriguez-Arboli
Department of Hematology, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS/CSIC/CIBERONC), University of Seville, Seville, Spain

*These authors contributed equally to this work.

Introduction

Acute myeloid leukaemia (AML) is the most common form of acute leukaemia in adults, with an incidence ranging from 5 to 8 per 100,000 in Europe[1] and with a current 5-year survival rate of 28.7%.[2]

The treatment of relapsed/refractory (R/R) AML represents a formidable challenge for treating clinicians. Intensive chemotherapy is usually recommended for fit patients to achieve a second complete remission (CR) to proceed to haematopoietic stem cell transplantation (HSCT). However, this approach commonly fails due to the patient's complexity.[3] In those patients who are not eligible for induction chemotherapy, hypomethylating agents (HMAs), that is, decitabine (DEC) or azacytidine (AZA), have been shown to be beneficial[4,5] but, in the salvage setting, are mainly used as palliative treatment. Novel noncytotoxic approaches have been recently developed due to a better understanding

of the molecular complexity and biology of AML. Targeted agents such as ivosidenib (IDH1 mutation),[6] enasidenib (IDH2 mutation)[7] and gilteritinib (FLT3 mutation)[8] have been shown to be effective in treating R/R patients with specific mutations.

Venetoclax (VEN) is a selective, orally bioavailable inhibitor of the antiapoptotic protein B-cell lymphoma 2 (BCL-2) with activity in a variety of haematologic malignancies.[9–11] As BCL-2 overexpression is associated with AML cell survival and treatment resistance,[12] BCL-2 inhibitors have the potential to sensitize AML cells to HMA,[13] thereby providing the rationale for combining VEN with HMA.

The US Food and Drug Administration has accelerated the approval of VEN in combination with HMA for adults who are 75 years of age or older or who have comorbidities and cannot use intensive induction chemotherapy. The clinical trial that motivated this approval was a phase I/II clinical trial of VEN + AZA or DEC in previously untreated AML patients older than 65 years who are not candidates for intensive therapy that showed CR + complete remission with incomplete haematologic recovery (CRi) rate of 73% with a median overall survival (mOS) of 17.5 months.[14] Subsequently, the phase III trial (VIALE-A) results were published, in which an OS of 14.7 months in the AZA–VEN group and an overall response rate (ORR) of 66.4% were obtained.[15]

The combination of VEN and HMA has not been systematically tested in R/R AML. Furthermore, AML is the most common form of acute leukaemia in adults, with a median age at diagnosis of 68 years.[16] Therefore, the vast majority of evidence published related to R/R AML is based on results obtained from the elderly population. Nevertheless, data concerning young patients have not been clearly defined and documented.

This study aims to review the available evidence in refractory AML patients treated with the VEN + HMA combination, specifically in young adult patients. In addition, we report two cases of young patients successfully treated in our centre with VEN + HMA.

The search was performed in the MEDLINE database using the following key terms: 'acute myeloblastic leukaemia', 'azacytidine', 'decitabine', 'venetoclax', 'relapse' and 'refractory'.

VEN combination therapy in R/R AML patients

In the R/R setting, VEN combination therapy with HMA is an option for unfit patients and those who are unlikely to benefit from standard salvage treatment due to recurrence after heterogeneous HSCT and high-risk genetic factors as complex cytogenetics, mononuclear karyotype, TP53 mutations and so on.

Data on VEN combination therapy are mainly limited to retrospective studies and one clinical trial (Table 1). A total of 16 observational studies of VEN + HMA combination therapy for R/R AML patients were identified (15 retrospective and 1 prospective) and 1 phase 1 clinical trial.[17–33] Of them, 16 included adults,[17–31,33] the majority being elderly patients, and only one study focused on paediatric patients and young adults.[32]

Five hundred sixty-four patients were treated in 17 studies, 177 (31.38%) patients received VEN + AZA and 320 (56.73%) received VEN + DEC. In the different studies, the ORR was mainly evaluated in the population as a whole.

The efficacy results obtained in these studies ranged from an ORR between 21.0%[18] and 92.0%.[30] mOS ranged from 3[18] to 11 months.[22] 12.59% ($n = 71$) of the patients received an allogeneic HSCT after treatment with VEN in combination. These results should be interpreted with caution because the number of patients included in these studies was small (median: 32, range: 8–90 patients), and treatment regimens, patient population and clinical response were heterogeneous (Table 2).

Regarding safety data, the most common adverse events (AEs) reported were haematologic or infectious AEs. These AEs were also the most commonly reported severe AEs (Table 1).

VEN combination therapy for young R/R AML patients

Traditionally, young AML patients achieve higher remission rates after chemotherapy compared

Table 1. Clinical studies with VEN combination therapy in relapsed/refractory AML.

Study	Design	*N*	R/R AML	Dosage, *n* (%)	Efficacy, *n* (%)	Toxicity, *n* (%)	Post-VEN combination HSCT
Aldoss and colleagues[17]	RETRO	33	33	VEN + AZA, 2 (6.1%) VEN + DEC, 16 (48.5%)	ORR: 21 (64%) CR: 10 (30%) CRi: 7 (21%) MLFS: 4 (12%) 1-year OS: 53%	Sepsis 11 (33.3%) Pneumonia 5 (15.2%) Colitis and diarrhoea 3 (9%) Atrial fibrillation 2 (6%) Acute renal failure 2 (6%)	3 (9.1%)
DiNardo and colleagues[18]	RETRO	43	39	VEN + AZA, 8 (18.6%) VEN + DEC, 23 (53.5%) VEN + LDAC, 8 (18.6%) VEN + Other, 4 (9.3%)	ORR: 9 (21%) CR: 2 (4.7%) CRi: 3 (6.5%) MLFS: 4 (9.3%) mOS: 3 (0.5–8) months	G ⩾ 3 neutropenia 43 (100%) G ⩾ 3 infection 31 (72%)	2 (5%)
Aldoss and colleagues[19]	RETRO	90	90	VEN + AZA, 9 (10%) VEN + DEC, 81 (90%)	CR/CRi: 41 (46%) CR: 23 (26%) CRi: 18 (20%) mOS: 7.8 months	N/A	14 (1.5%)
Aldoss and colleagues[20]	RETRO	31	16	VEN + AZA, 3 (9.7%) VEN + DEC, 28 (90.3%)	CR/CRi: 16 (51.6%) CR: 7 (22.6%) CRi: 9 (29.0%) mOS: 11 months	N/A	5 (16.1%)
Asghari and colleagues[21]	RETRO	31	31	VEN, 1 (3.2%) VEN + AZA, 13 (41.9%) VEN + DEC, 17 (54.8%)	ORR: 10 (34.5%) CR: 0 (0%) CRi: 8 (27.6%) MLFS: 2 (6.9%) mOS: 4.9 months	N/A	2 (6.5%)
Mittal and colleagues[22]	RETRO	11	11	VEN + AZA, 8 (72.7%) VEN + DEC, 3 (27.3%)	CR/CRi: 4 (36%) PR/SD: 5 (45%) mOS: 11 months	N/A	N/A
Ram and colleagues[23]	PROSP	23	23	VEN + AZA, 16 (69.6%) VEN + DEC, 4 (17.4%) VEN + LDAC, 3 (13%)	CR/CRi: 10 (43%) CR: 5 (21.7%) CRi: 5 (21.7%) 6-month mOS: 74% mOS: 5.6 months	Febrile neutropenia 18 (78%)	1 (4.35%)
Aldoss and colleagues[24]	RETRO	50	33	VEN + AZA, 2 (6%) VEN + DEC, 31 (94%)	CR/CRi: 14 (42%) mOS: 8.33 months	N/A	8 (24.24%)
Byrne and colleagues[25]	RETRO	21	21	VEN + AZA, 12 (57.1%) VEN + DEC, 4 (19%) VEN + LDAC, 5 (23.8%)	ORR: 8 (42.1%) CR: 5 (26.3%) CRi: 3 (15.8%) PR: 0 (0%) MLFS: 4 (21.1%) mOS: 7.8 months	Infectious complications 13 (61.9%)	4 (19.1%)
DiNardo and colleagues[26]	Phase 2b RCT	168	55	VEN + DEC, 55 (100%)	CR/CRi: 23 (42%) CR: 13 (24%) CRi: 10 (18%) mOS: 7.8 (5.4–13.3) months	G3 infections 79 (47%) G4 neutropenia 79 (47%) Febrile neutropenia 49 (29%)	10 (18.2%)

(continued)

Table 1. (continued)

Study	Design	*N*	R/R AML	Dosage, *n* (%)	Efficacy, *n* (%)	Toxicity, *n* (%)	Post-VEN combination HSCT
Gaut and colleagues[27]	RETRO	14	14	VEN + AZA, 8 (57.1%) VEN + DEC, 5 (35.7%) VEN + LDAC, 1 (7.1%)	ORR: 35.7% CR: 3 (60%) PR: (2 (40%) mOS: 4.7 months	Grade 3/4: Infection 7 (50%) Intracranial haemorrhage 3 (21.4%)	3 (21.4%)
Lou and colleagues[28]	RETRO	48	48	VEN + AZA, 48 (100%)	ORR: 23 (47.9%) CR: 14 (29.2%) CRi: 9 (18.8%)	Grade 3/4: Neutropenia 44 (92%) Thrombocytopenia 43 (90%)	6 (12.5%)
Morsia and colleagues[29]	RETRO	86	42	VEN + AZA, 8 (19%) VEN + DEC, 35 (83.3%)	CR/CRi: 14 (33.3%) CR: 8 (19.1%) CRi: 6 (14.3%) mOS: 5 (3–9) months	N/A	N/A
Tiong and colleagues[30]	RETRO	12	12	VEN + AZA, 3 (25%) VEN + LDAC, 9 (75%)	CR: 11 (92%)	G3 nonhaematological toxicities 2 (17%)	3 (25%)
Wang and colleagues[31]	RETRO	40	40	VEN, 8 (20%) VEN + AZA, 21 (52.5%) VEN + LDAC, 10 (25%) VEN + FLAG, 1 (2.5%)	ORR: 20 (50%) CR: 5 (12.5%) CRi: 4 (10%) MLFS: 5 (12.5%) PR: 6 (15%) mOS: 6.6 months	Febrile neutropenia 27 (75%) Infections 18 (45%)	6 (15%)
Winters and colleagues[32]	RETRO	8	8	VEN + AZA, 8 (100%)	ORR: 6 (75%) CR: 3 (37.5%) MLFS: 1 (12.5%) <5% blasts: 2 (25%)	G4 neutropenia 8 (100%) G4 thrombocytopenia 8 (100%)	4 (50%)
Joshi and colleagues[33]	RETRO	29	29	VEN, 1 (3.4%) VEN + AZA, 8 (27.6%) VEN + DEC, 18 (62%) VEN + LDAC, 1 (3.4%) VEN + gilteritinib, 1 (3.4%)	ORR: 11 (38%) CR/CRi: 8 (28%) PR: 3 (10%) mOS: 2.6 (0.1–13.4) months	G3/4: Neutropenia 20 (69%) Thrombocytopenia 19 (65.5%) Infections 16 (55.2%) Anaemia 15 (51.7%)	N/A

AML, acute myeloid leukaemia; AZA, azacytidine; CR, complete remission; CRi, CR with incomplete haematologic recovery; DEC, decitabine; FLAG, Fludarabine-Arabinofuranosyl cytidine- Granulocite colony-stimulating factor; HSCT, haematopoietic stem cell transplantation; LDAC, low-dose cytarabine; MLFS, morphologic leukaemia-free state; mOS, median overall survival; N/A, not available; ORR, overall rate response; PR, partial remission; PROSP, prospective study; RCT, randomized controlled trial; RETRO, retrospective study; R/R, relapse/refractory; SD, stationary disease; VEN, venetoclax.

Table 2. Patients' baseline characteristics.

Study	*N*	mAge (range)	Male, *n* (%)	Diagnosis/AML type	Refractory, *n* (%)	Relapsed, *n* (%)	Cytogenetics, *n* (%)	ELN risk stratification, *n* (%)	Prior ASCT, *n* (%)	Prior lines Median (range)
Aldoss and colleagues[17]	33	62 (19–81)	15 (45.5%)	*De novo* 23 (69.7%) Secondary 5 (15.2%) t-AML 5 (15.2%)	11 (33.3%)	FR: 14 (42.4%) SR: 8 (24.2%)	Good 3 (9%) Intermediate 11 (33%) High 18 (55%) Unknown 1 (3%)	N/A	13 (39.4%)	2 (1–8)
Dinardo and colleagues[18]	43	68 (25–83)	28 (65%)	AML 39 (91%) MDS/MPN 2 (5%) BPDCN 2 (5%)	43 (100%)	First: 7 (16%) Second: 36 (84%)	Adverse 20 (47%) Diploid 12 (28%) Invasive (16) 2 (5%) Intermediate 9 (21%)	N/A	5 (12%)	3 (1–6)
Aldoss and colleagues[19]	90	59 (18–81)	46 (51%)	*De novo* 58 (64%) t-AML 10 (11%) Secondary 22 (24%)	N/A	N/A	N/A	Fav/Interm 31 (34%) Adverse 59 (66%)	26 (29%)	2 (1–8)
Aldoss and colleagues[20]	31	68 (22–85)	14 (45%)	*De novo* 13 (42%) Secondary/t-AML 18 (58%)	16 (52%)	N/A	Complex 24 (77%) Normal 2 (6%) Others 5 (16%)	N/A	5 (16%)	N/A
Asghari and colleagues[21]	31	63 (25–77)	13 (41.9%)	AML-MRC 19 (61.3%) t-AML 3 (9.7%) Other AML 9 (29%)	N/A	N/A	N/A	Fav/Interm 8 (26%) Adverse 14 (45%) N/A 9 (29%)	N/A	2 (1–6)
Mittal and colleagues[22]	11	66 (25–75)	N/A	R/R *de novo* or secondary AML or progressive MDS following ASCT	N/A	N/A	N/A	N/A	11 (100%)	N/A
Ram and colleagues[23]	23	76 (41–92)	14 (60.9%)	AML-RGA 3 (13%) AML-MRC 10 (44%) t-AML 5 (22%) AML NOS 5 (22%)	23 (100%)	FR: 6 (26.1%)	Normal 11 (48%) Complex 6 (26%)	Favourable 2 (9%) Intermediate 11 (48%) High risk 10 (43%)	6 (26%)	2 (1–5)
Aldoss and colleagues[24]	50	58 (18–77)	16 (48%)	*De novo* 25 (76%) Secondary/t-AML 8 (24%)	N/A	N/A	N/A	Favourable 1 (3%) Intermediate 23 (70%) High 9 (27%)	9 (27%)	2 (1–7)
Byrne and colleagues[25]	21	64.5 (35–74)	13 (61.9%)	CMML 1 (4.8%) MDS 3 (14.3%) PMF 1 (4.76%) AML 16 (76.19%)	N/A	FR: 21 (100%)	Normal 2 (9.5%) Complex 2 (9.5%) Not complex 1 (5%) Adverse 4 (19%) Intermediate 11 (52%) Favourable 1 (5%)	N/A	21 (100%)	N/A
DiNardo and colleagues[26]	168	62 (43–73)	31 (56%)	*De novo* 51 (93%) t-AML 4 (7%)	55 (32.7%)	N/A	Favourable 0 Intermediate 32 (58%) Adverse 23 (42%)	Favourable 8 (15%) Intermediate 12 (22%) Adverse 35 (64%)	18 (33%)	2 (1–3)

(continued)

Table 2. (continued)

Study	*N*	mAge (range)	Male, *n* (%)	Diagnosis/AML type	Refractory, *n* (%)	Relapsed, *n* (%)	Cytogenetics, *n* (%)	ELN risk stratification, *n* (%)	Prior ASCT, *n* (%)	Prior lines Median (range)
Gaut and colleagues[27]	14	58 (41–79)	11 (78.6%)	*De novo* 9 (64.3%) Secondary 5 (35.7%)	7 (50%)	FR: 5 (35.7%) SR: 2 (14.3%)	Intermediate 4 (28.6%) Adverse 10 (71.4%)	N/A	3 (21.4%)	3 (1–8)
Lou and colleagues[28]	48	61 (19–73)	28 (58.3%)	R/R AML 48 (100%)	16 (33.3%)	FR: 21 (43.8%) SR: 27 (56.2%)	N/A	Favourable 7 (14%) Intermediate 21 (44%) Adverse 20 (42%)	N/A	N/A
Morsia and colleagues[29]	86	73.5 (37–91)	27 (61.4%)	*De novo* 20 (47.6%) Secondary 15 (35.7%) t-AML 7 (16.7%)	25 (59.5%)	FR: 13 (31%) SR: 4 (9.5%)	N/A	Good 5 (11%) Intermediate 12 (27%) Poor 27 (62%)	N/A	2 (1–5)
Tiong and colleagues[30]	12	60.5 (29–81)	7 (58.3%)	R/R AML 12 (100%)	5 (41.7%)	FR: 6 (50%) SR: 1 (8.3%)	Normal (91.6%) Complex (8.33%)	N/A	1 (8.3%)	3 (1–6)
Wang and colleagues[31]	40	63 (20–88)	26 (65%)	*De novo* 25 (62.5%) Secondary 13 (32.5%) t-AML 2 (5%)	N/A	N/A	Favourable 1 (2.5%) Intermediate 25 (62.5%) Unfavourable 11 (27.5%) Unknown 3 (7.5%)	Favourable 5 (12%) Intermediate 7 (18%) Unfavourable 28 (70%)	13 (32.5%)	3 (1–9)
Winters and colleagues[32]	8	11 (2–20)	4 (50%)	AML 5 (62.5%) MDS/AML 1 (12.5%) MDS 2 (25%)	2 (25%)	FR: 3 (37.5%)	Normal 3 (37.5%) Complex 2 (25%)	N/A	N/A	N/A
Joshi and colleagues[33]	29	58 (20–72)	14 (48%)	*De novo* 11 (38%) Secondary 5 (17%) t-AML 3 (10%) High-risk MDS 10 (35%)	4 (14%)	FR: 21 (72%) SR: 4 (14%)	Favourable 1 (3%) Intermediate 10 (35%) Adverse 18 (62%)	N/A	29 (100%)	2 (1–4)

AML, acute myeloid leukaemia; AML-MRC, acute myeloid leukaemia with myelodysplasia-related changes; AML-RGA, acute myeloid leukaemia with recurrent genetic abnormalities; ASCT, autologous stem cell transplant; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CMML, chronic myelomonocytic leukaemia; ELN, European LeukemiaNet; Fav/Interm, favourable/intermediate; FR, first relapsed; mAge, median age expressed in years; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; N/A, not available; NOS, not otherwise specified; PMF, primary myelofibrosis; R/R, relapse/refractory; t-AML, therapy-related AML; SR, second relapsed.

with elderly patients. The most common definition of a young patient in the AML population is younger than 60 years, with slight differences between the studies. However, there is a wide age range from 18 to 60 years, between which there may be differences that explain the different responses obtained to the same drug.

A group of young AML patients which are usually studied separately is the group of adolescents and young adults, which encompass a group of the population that arbitrarily combines paediatric and adult patients with an age range of 15–39 years[34]

The currently available evidence of VEN combination therapy for young R/R AML patients is scarce. Of the 17 studies we have identified, only 1 focuses on paediatric and young adult patients. Of the remaining studies, 12 (70.6%) included a population with a median age more than 60 years.

Winters and colleagues[32] is the only study identified on the VEN + AZA combination that includes paediatric patients ($n = 6$) and young adults ($n = 2$). Of the two young adult patients identified, the first (18-year-old woman) achieved a morphologic leukaemia-free state. This patient presented *FLT3-ITD, WT1* and *NUP98/NSD1* mutations. The other patient (30-year-old man) with the following cytogenetic alterations 3 46, XY, t (2; 14) (q22; q32) and the following mutations *FLT3-TKD, WT1, BCORL1, GATA2* reached complete response, with negative molecular measurable residual disease (MRD) subsequently being able to receive an allogeneic transplant.

Here, we report two cases of AML refractory young patients treated with VEN + HMA.

Case 1

We report the case of a 26-year-old woman. In August 2018, she was diagnosed with monocytic AML [t (6; 11), mixed-lineage leukaemia (MLL) positive, FLT3-ITD negative]. She was treated with conventional chemotherapy following the '3 + 7' scheme and '2 + 5' scheme. She achieved complete haematological and molecular remission with negative MRD.

In February 2019, she received an allogeneic HSCT from a matched related donor with a myeloablative conditioning regimen with busulfan and cytarabine (BuCy). The patient was in a CR situation with a positive molecular MRD post-HSCT. She suffered hepatic graft-*versus*-host disease (GvHD) as a complication associated with the HSCT.

In December 2019, she was hospitalized with a non-neutropenic febrile syndrome of amygdalar focus, diagnosed with a medullary relapse of her AML. She was treated with reinduction chemotherapy following the FLAGQUIDA scheme (FLAGIDA + quizartinib 40 mg) within a clinical trial. Postinduction CR with complete chimerism and negative molecular MRD was reached. As complications of reinduction treatment, she presented invasive pulmonary aspergillosis and cutaneous GvHD. She received consolidation chemotherapy with high-dose cytarabine and maintenance chemotherapy with quizartinib.

In March 2020, an MRD positivization was detected, and she was treated with two donor lymphocyte infusions (DLIs) in June and July. After the first dose, in June 2020, a medullary control was performed and revealed an overt relapse.

In July 2020, she started treatment with AZA (75 mg/m^2, days 1–7 of each 28-day cycle) for two cycles without response. Antifungal prophylaxis with posaconazole was also started. Three months later (October 2020), she started combination treatment with AZA + VEN (uptitrated from 100 mg daily to a maximum dose of 400 mg). Antifungal prophylaxis with posaconazole was withdrawn due to potential interaction with VEN treatment. She presented asthenia as the main adverse effect associated with the treatment.

A third DLI was administered in September 2020. After two cycles (November 2020), she was hospitalized due to an episode of febrile neutropenia with a probable rectal-perianal focus, and VEN treatment was withheld. She was treated with broad-spectrum antibiotics. During admission, antifungal prophylaxis with posaconazole was reinstated. At the beginning of December, treatment response was evaluated by a bone marrow biopsy, obtaining a result of CRi.

In January 2021, another bone marrow biopsy was performed, revealing 57% of the myeloblast. After this result, it was decided to restart AZA + VEN treatment (third cycle). VEN dose

was uptitrated from 50 mg to a maximum dosage of 70 mg due to concomitant use of posaconazole and previous myelosuppression.

After this treatment cycle, she was admitted for intravenous antibiotic therapy administration due to a persistent superinfected whitlow in the first toe of both feet, despite oral antibiotic therapy. Treatment with VEN was withheld until recovery from infection. After recovery, the patient restarted with VEN in combination with AZA at a dose of 100 mg/day and completed another cycle of treatment.

In March 2021, a bone marrow biopsy was performed, revealing disease progression with 57% of the myeloblast. A month later, she was hospitalized due to febrile syndrome. Due to the underlying disease development, a multiple organ failure caused her death 12 days later.

Case 2

We report the case of a 47-year-old woman. In April 2018, she was diagnosed with AML with myelodysplasia-related changes with complex karyotype including del5q, delTP53, trisomy 8 and three copies of MLL, nonmutated FLT3, TP53 and PTPN11 mutations.

She was treated with induction chemotherapy following the '3 + 7' scheme without treatment response. Then, she received rescue treatment with guadecitabine within a clinical trial (SGI-110-06). After three cycles of chemotherapy, CR with negative MDR was reached. During these admissions, she presented notable complications such as gangrenous appendicitis that required appendectomy in May 2018 and a paracolic abscess with inflammatory changes in the cecum and right colon with colic and ileal fistulization that required a right hemicolectomy in September 2018.

In December 2018, she received an allogeneic HSCT from a matched related donor with a reduced-intensity conditioning regimen with fludarabine and busulfan and GvHD prophylaxis with tacrolimus and rapamycin. As posttransplant complications, she presented grade 2 cutaneous GvHD and pasty stools with irregular bowel habits. The results of endoscopy with biopsy were not suggestive of intestinal GvHD.

Approximately 3 months later, she presented positive MRD in the marrow (0.5% of blasts). Treatment with AZA (75 mg/m^2, days 1–7 of each 28-day cycle) and decreased immunosuppression were indicated.

In June 2019, a medullar study revealed an overt relapse. Combination treatment with VEN (uptitrated from 100 mg daily to a maximum dose of 400 mg) and DEC (20 mg/m^2 × days 1–5 of each 28-day cycle) and rapid immunosuppression withdrawal were initiated. After the first cycle of VEN + DEC, she reached CRi with positive MRD. As treatment complications, she presented myelosuppression and required admission due to febrile neutropenia. Treatment with VEN was withheld during hospitalization and was subsequently restarted at a dose of 100 mg per day due to cytotoxicity and possible interaction with antifungal prophylaxis with posaconazole.

During treatment with VEN + DEC, she presented primary *Escherichia coli* bacteremia with possible secondary splenic abscess and possible disseminated candidiasis, initially treated with caspofungin administered via outpatient parenteral antimicrobial therapy followed by oral voriconazole. During treatment with voriconazole, the VEN dose was reduced to 70 mg due to possible interaction.

After five cycles of combination therapy, it was decided to suspend the combination treatment due to myelosuppression and the associated risk of infectious complications after reaching CR and negative MRD. A second related donor transplant was considered, although it was finally decided to prophylactically perform a DLI to maintain CR with negative MRD and complete chimerism.

The patient remained without treatment until August 2020, when the level of myeloblast reached 40%. Then, it was decided to restart treatment with DEC + VEN (100 mg per day due to risk of interaction with posaconazole treatment) before performing a second HSCT. In September, she was admitted, with diarrhoea and fever being diagnosed with community-acquired pneumonia with *Klebsiella pneumoniae* isolation. After 8 days of hospitalization in the intensive care unit, the patient died of septic shock due to pneumonia.

Discussion

Treatment of R/R AML remains a formidable challenge for treating clinicians because of the high failure rate of reinduction treatment characterized by a short survival period with OS estimated not more than 10% at 3 years and progressive complications.[35,36]

As a result of this review, VEN combination treatment with HMAs appears to be a therapeutic option for R/R AML. Nevertheless, ORR described in the literature is very heterogeneous, ranging from 21.0% to 92.0% and mOS between 3 and 11 months among adult patients. Regarding the efficacy of this treatment for young patients, it is difficult to draw conclusions because most of the patients included in the studies were elderly patients, and the results were not expressed by age subgroups. Usually, the elderly AML population achieves lower remission rates (40–50%) after chemotherapy compared with young patients (60–70%).[37,38] Thus, the efficacy of VEN combination therapy is expected to be similar or superior to that obtained in elderly patients, as in the case of Winters and colleagues,[32] which obtained an ORR of 75%. However, there is no solid evidence to make a firm conclusion for VEN combination therapy for young AML patients at present. In fact, our patients obtained limited success with this combination regimen. Concerning safety, haematologic or infectious adverse reactions were the most frequently reported. The incidence of adverse reactions reported for VEN combination therapy was higher than that reported for HMA monotherapy.[15]

VEN + HMA regimen has been used in naïve[15] and R/R patients,[17–31,33] being a therapeutic alternative in patients who are not candidates for HSCT. This review showed that most patients were treated with VEN + HMA as a salvage approach previous to an HSCT; however, we found several studies that included previously transplanted patients. Focusing on those studies, we observed response rates of 36%,[22] 38%[33] and 42.1%[25] and mOS of up to 11 months.[22] Although the results in this group of patients may be discrete compared with those obtained in patients who have not previously received an HSCT, this scheme may be an option for patients with few therapeutic alternatives. Moreover, at our centre, this treatment combination was used on patients who were refractory to a first HSCT. Thus, the VEN + HMA combination could be a salvage approach for refractory patients before and after receiving an HSCT or when this procedure is not feasible.

However, these approaches should be tested on well-designed randomized controlled trials that compare VEN + HMA and conventional chemotherapy. Therefore, in the absence of quality evidence, the clinician should assess this combination therapy's benefit/risk balance with AML patients.

A significant aspect of this combination is its high response rate across various cytogenetics and almost all molecular subtypes of AML. Among the studies included in this review, an excellent clinical activity for this combination has been obtained even for patients with high-risk cytogenetics or poor prognosis. Mutations with increased sensitivity to VEN + HMA therapy have been identified, such as IDH1, IDH2, NPM1, RUNX1 and SRSF2.[14,17,18,31,32]

As bridging therapy before HSCT, VEN + HMA combination is not associated with significant toxic effects beyond cytopenias, so a considerable increase in adverse effects associated with pretransplant conditioning regimens or prophylaxis regimens for GvHD management is not initially expected. Compared with patients receiving intensive salvage chemotherapy, it is expected that patients undergoing HSCT after HMA + VEN treatment, especially in the case of R/R AML, will have a better performance status and reduced morbidity.[39]

Given that the primary toxicity of the VEN + HMA combination treatment is peripheral blood cytopenias, the potential for accumulated risk of infections after HSCT may be a concern. This can be notably true for invasive fungal infections (IFIs) because affected patients might be undergoing HSCT with occult or evident IFIs. The risk of IFIs seems to be low in patients receiving VEN + HMA treatment for first-line AML treatment; however, patients with R/R AML might be at higher risk.[40]

One of the uncertain areas in the treatment of AML with VEN is the routine use of antifungal prophylaxis. VEN is a CYP3A4 substrate, so there is a risk of potential interaction with drugs used in antifungal prophylaxis in patients with

haematologic malignancies such as azoles which are CYP3A4 inhibitors. Patients receiving antifungal prophylaxis usually require dosing modification for safe VEN use. Both of our patients receive antifungal treatment with posaconazole (patients 1 and 2) and voriconazole (patient 2) with a consequent reduction of VEN doses to reduce AE risk. For both patients, a 75% reduction on VEN dose was applied when they started posaconazole treatment. For patient 2, an additional reduction of 82.5% of the initial dose was applied. Both patients benefitted from the dose adjustments, reducing the adverse effects associated with the treatment. Clinical trials usually exclude patients treated with CYP3A4 inhibitors due to potential interactions. However, a phase 1b trial included an arm receiving posaconazole prophylaxis to evaluate the pharmacokinetics interaction. The recommendation was to perform a 75% dose reduction of VEN when given simultaneously with posaconazole.[41] Mei and colleagues[42] recommend reducing VEN dose by 50% for patients receiving treatment with moderate CYP3A4 inhibitors, such as isavuconazole, and 75% for patients receiving potent CYP3A4 inhibitors, such as posaconazole or voriconazole. At the moment, we routinely use posaconazole as antifungal prophylaxis, even when isavuconazole is usually better tolerated and has fewer interactions than other azoles.[43] Isavuconazole, however, may also worsen myelosuppression due to increased levels of VEN, despite being a moderate CYP3A4 inhibitor. So far, there is no evidence that the use of isavuconazole is preferable to posaconazole concomitantly with VEN. Rauch and colleagues study showed that the concomitant use of azoles with the VEN + HMA regimen resulted in similar absolute neutrophil count and platelet recovery times, suggesting that the azole used is indifferent as long as the appropriate VEN dose reduction is applied.[44] Unfortunately, there are no techniques to monitor VEN serum levels at present in clinical practice.[43]

In our centre, generally, for treating young AML patients, we use the FLAGIDA scheme as the first rescue option, as was done in the case of patient 1. With the FLAGIDA scheme, a CR/CRi of 51% in patients younger than 60 years and an mOS of 0.8 years (0.6–1.4) have been obtained.[45] In patients with TP53 mutations with elevated variant allele frequency (VAF), the use of conventional chemotherapy *versus* VEN + HMA may be more debatable. There are conflicting results in the literature for patients with this mutation; in the study by Short and colleagues,[46] the VEN + HMA scheme was ineffective in *de novo* patients. However, in the VIALE-A trial,[15] patients with the TP53 mutation appeared to benefit from the combined treatment.

We report two young patients with R/R AML who achieved CR and negative MRD after treatment with a VEN + HMA regimen. Both patients achieved CR after the first two cycles of treatment which was consistent with other retrospective studies of VEN combination therapy for R/R AML, where the best response was found after a median of two cycles (range 1–3) and one cycle at the earliest.[9,15,17,18,41] Knowing this average response time can help stop treatment prematurely if no response is found. In turn, this may help reduce some of the AEs caused by long-term VEN combination therapy. Mei and colleagues[42] recommend a bone marrow biopsy to assess response only after two cycles of therapy, as at this point, the majority of CR is recorded.

As the main adverse reactions associated with combination treatment, both patients suffered myelosuppression, asthenia and infections which are consistent with those reported in previous studies.[17,18,23,25–28,30–32] In both cases, treatment withhold was required due to cytopenia and the associated high risk of infections. For patient 1, VEN treatment was interrupted after two cycles due to a febrile neutropenia episode. The patient was in CRi when the treatment was interrupted. After almost 3 months without treatment, her blast increased to 57%. Mei and colleagues[42] recommend not interrupting therapy, delaying cycles or reducing dose based on peripheral blood cytopenia, marrow hypocellularity or aplasia before achieving maximal response because this may reduce the depth and speed of response. This may explain why patient 1 took so long to achieve CR, as she was required to suspend treatment several times due to toxicity. For patient 2, it was decided to suspend treatment for a while after reaching CR due to the high associated risk of infections.

In our centre, we make dose adjustments once the patient has obtained a remission, or at least, we confirm aplasia without blasts. However, these patients often already have baseline G3-4 cytopenias due to the disease's nature, so the impact of dose adjustment in these cases may be limited.[14]

Despite the promising efficacy results obtained with VEN combination treatment, its toxicity and potential interactions are limiting factors. Furthermore, the degree of cytopenias reported in refractory AML patients is higher than that reported in naïve-treatment patients, possibly due to higher rates and degrees of cytopenias before VEN combination treatment administration.[14,18]

The results presented in this brief review should be interpreted cautiously due to the heterogeneity of patients and regimens used, the relatively low quality of the available evidence, based essentially on retrospective observational studies, and the lack of results expressed by age subgroups. Further controlled clinical trials are needed to prove whether VEN + HMAs combination is an adequate alternative to conventional regimens for young R/R AML patients.

As limitations of the study, we highlight that a systematic review method was not followed to review the available literature; however, an exhaustive search of the literature was conducted in MEDLINE and Embase databases. However, the synthesis of the evidence performed was qualitative, given the heterogeneity of the available studies. Given the heterogeneity between studies, quantitative synthesis of the evidence could not be developed currently.

In summary, we provide a review of the available evidence on the treatment of VEN in combination with HMA for the treatment of young R/R AML patients, in addition to our experience in clinical practice. VEN + HMA seems to be a therapeutic option for treating young adult R/R AML patients. Notwithstanding, due to the limited quality of the available evidence, well-designed studies with greater numbers of patients are needed to confirm the efficacy and safety of VEN combination regimens for young patients with R/R AML.

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Consent for publication

Due to the fact that both patients died, it was not possible to request their consent for the publication of the cases.

Ethical approval statement

According to the local regulations, approval by the local ethical committee is not required for publication of case reports because all patient-related data were collected retrospectively and anonymously.

ORCID iD

Nerea Báez-Gutiérrez https://orcid.org/0000-0002-9419-7742

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