

Impact of infectious comorbidity and overall time of hospitalization in total outpatient management of acute myeloid leukemia patients following venetoclax and hypomethylating agents

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Abstract

Venetoclax (VEN) and hypomethylating agent (HMAs) regimens are emerging as the standard of care for unfit for chemotherapy acute myeloid leukemia (AML) patients, but the safety and feasibility of a total outpatient management have not been fully investigated. Fifty-nine AML patients with active disease received VEN and HMAs. Nineteen out of 59 (32.2%) patients received the first cycle as inpatients, whereas 40/59 (67.8%) patients were treated in the outpatient setting. No significant differences were observed with regard to incidence of adverse events (AEs), including tumor lysis syndrome (TLS), and the 30-day and 60-day mortality was comparable. Notably, an infectious prophylaxis inspired to that adopted during intensive chemotherapy resulted in a low infection rate with a reduced bacterial infections incidence in out- versus hospitalized patients ($p < .0001$). The overall time of hospitalization was significantly shorter in patients who received a total outpatient treatment as compared to those who received the first cycle as inpatients (5.9 vs. 39.7 days, $p < .0001$). Despite the adopted differences in treatment management, the efficacy was similar. These data indicate that a total outpatient management of VEN and HMAs is feasible in AML patients without negatively impacting on treatment efficacy and may yield pharmaco-economic and quality-of-life benefits.

Cristina Papayannidis and Jacopo Nanni contributed equally.

Novelty statement: Venetoclax (VEN) and hypomethylating agents (HMAs) regimen is rapidly emerging as the standard of care for unfit-to-chemotherapy acute myeloid leukemia (AML) patients. Hospitalization negatively affects the quality of life of patients with cancer, including AML, and may be associated with more severe complications such as infections. To the best of our knowledge, no data have been reported about the safety and feasibility of a total outpatient management of AML patients following VEN and HMAs regimen. Our real-life study highlights that such approach is feasible without negatively impacting on treatment efficacy and may yield pharmaco-economic and quality-of-life benefits.

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**KEYWORDS**

acute myeloid leukemia, hospitalization, hypomethylating agents, infections, outpatient, real life, Venetoclax

1 | INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease arising from a rare population of leukemic stem cells and leading to the clonal expansion and accumulation in the bone marrow (BM) of neoplastic immature myeloid cells with impaired differentiation capacity.¹ In the recent years, new and effective agents have entered the clinical stage in the attempt to improve the outcome of AML patients, whose prognosis is largely unsatisfactory mainly due to a still high rate of relapse.² Among them, Venetoclax (VEN), a highly selective and orally bioavailable BCL2 inhibitor, represents a major breakthrough. In particular, Phase II and III clinical trials have clearly demonstrated the efficacy of VEN in combination with low-dose cytarabine (LDAC) or hypomethylating agents (HMAs) in newly diagnosed AML patients, who are not fit for intensive chemotherapy.^{3,4}

Hospitalization negatively affects the quality of life of patients with cancer, including leukemias, and may be associated with a higher risk of complications, such as infections.⁵⁻⁷ Moreover, hospitalization significantly impacts on the economic burden of AML patient management with differences that vary according to each national health system legislation. For all these reasons, there is a trend toward outpatient management of many conditions formerly thought to require inpatient care, including intensive AML induction chemotherapy.⁸ VEN plus HMA regimen administration is becoming the standard of care for unfit for chemotherapy AML patients. To the best of our knowledge, no data have been reported about the feasibility of a total outpatient management of such a frail population undergoing VEN plus HMAs treatment. In this scenario, the accumulation of new evidence regarding the impact of a total outpatient management of VEN plus HMA in the real-life setting and outside clinical trials may represent an important issue to guide future approaches and strategies for the treatment of elderly AML.

The purpose of this study was to evaluate the safety profile and clinical efficacy of a total outpatient management of the VEN plus HMA regimen for newly diagnosed (ND) and relapsed/refractory (R/R) AML patients, in comparison with the standard of care including an initial inpatient phase. Topic questions regarding the management of the combination therapy have been addressed.

2 | METHODS

2.1 | Study population

This is a retrospective single-center study enrolling patients with ND or R/R AML treated with VEN in combination with HMAs (azacitidine or decitabine) at Seràgnoli Hematology Institute of Bologna

between March 2018 and May 2021 (Ethical Committee code number: 112/2014/U/test).

2.2 | Treatment schedule and management

Patients received the standard schedule of 5-azacitidine (75 mg/m² s.c) on Days 1-7 or decitabine (20 mg/m² i.v.) on Days 1-5 of each 28-day cycle in combination with once-daily oral VEN. The choice of HMA was at the physician's discretion.

The dosage of VEN ranged from 50 to 400 mg, considering the concomitant azole therapy for fungal prophylaxis and evidence regarding drug interactions and appropriate dose adjustments.⁹ For patients receiving more than 100 mg of the drug, a ramp-up phase was conducted, based on clinical practice guidelines.²

According to Institution policy, the treatment regimen was administered ab initio within an outpatient plan. HMA therapy was administered in an outpatient clinic or, in very frail patients, at home by a specialist home care service (Details in Supplemental S1). Some patients received the first 28-day cycle of therapy as inpatients due to clinical reasons, such as ongoing complications of hematological disease or previous hematological treatments and were used as a comparison group.

2.3 | Evaluation criteria

In terms of effectiveness, clinical evaluation and blood count tests were used to monitor therapy in the majority of patients. While ND patients always received full bone marrow (BM) response evaluation, the latter was performed in selected cases among R/R patients. Criteria for BM evaluation in R/R patients were as follows: younger age, eligibility for hematopoietic stem cell transplantation (HSCT), and availability of experimental therapies as further salvage.

Responses were classified according to 2017 European Leukemia Net (ELN) response criteria.¹⁰ To define response, we collected data in Supplemental S2.

Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.¹¹

2.4 | Data and statistical analysis

Demographic data, disease features and prior therapeutic regimens, cytogenetic and molecular data, laboratory parameters, side effects, and their management with a special focus on tumor lysis syndrome and infections, response assessments during and after treatment,



and survival were retrospectively analyzed by accessing medical records.

Acute myeloid leukemia risk was stratified according to 2017 ELN risk stratification.¹⁰ Review of cytogenetic status included karyotype based on a minimum of 20 metaphase cells from the bone marrow or peripheral blood, if bone marrow analysis was not available. Abnormalities detected are listed in Supplemental S3. Molecular analyses were performed on DNA or RNA of mononucleated cells by polymerase chain reaction (PCR), or Sanger sequencing, or capillary electrophoresis and/or next-generation sequencing, as appropriate. The list of genes analyzed for mutational status is provided in Supplemental S3. Analyses were performed on the entire study population, if not otherwise specified. Rates and medians are reported descriptively with minimum and maximum. Therapy response is expressed as a rate. Survival was estimated with Kaplan–Meyer method and reported as a median. Subgroup analyses were conducted whenever appropriate. Comparison of the inpatient and outpatient cohorts' characteristics was made using the Wilcoxon rank sum test for numerical variables and Fisher's exact test for categorical variables. Kruskal–Wallis test has been used to compare medians of the two different study cohorts. The dataset (individual raw data) is available upon request.

3 | RESULTS

3.1 | Baseline patient and disease characteristics

A total of 59 AML patients received a combination of VEN plus HMA. Patients' and disease characteristics are shown in Table 1. The median age was 70 (range 22–88) years, 44/59 (74.6%) were male, 28.8% had a documented Eastern Cooperative Oncology Group (ECOG) 0, 55.9% ECOG 1, and 15.3% ECOG 2. The median number of VEN and HMAs therapy courses was 2 (range 1–9, IQR: 1.0–4.0). Overall, VEN was combined with azacitidine in 36/59 (61%) patients and with decitabine in 23/59 (39%) patients. In total, 27/59 (45.8%) patients had prior HMA exposure and 8/59 (13.6%) were treated after allogeneic-HSCT (allo-HSCT). Overall, 34/59 (57.6%) had a *de novo* disease, while 22/59 (37.3%) of patients were affected by a secondary AML (to MDS/MPN) and 3/59 (5.1%) had a therapy-related AML. With regard to risk stratification according to ELN 2017, 6/59 (10.2%) were in the favorable risk group, 28/59 (47.5%) and 22/59 (37.3%) in the intermediate and adverse risk one, respectively (Table 1, Table S1).

Forty-three patients were treated in the R/R setting, whereas 16 patients were ND. Main patients and disease characteristics at diagnosis and at the time of VEN combination therapy according to disease status are shown in Table S2.

Nineteen out of 59 (32.2%; 15/43 R/R, 4/16 ND) patients received the first cycle as inpatients, whereas 40/59 (67.8%; 28/43 R/R, 12/16 ND) patients were treated in the outpatient setting. Main demographic and disease variables were comparable between

in- and outpatients at therapy initiation, except for the median age, which was significantly lower in the inpatient R/R group (50 vs. 71 years, $p = .001$), the number of patients with ongoing antimicrobial therapy, which was higher in the inpatient group (both ND and R/R, 50% vs. 0% $p = .05$, and 60% vs. 3.6% $p = .001$, respectively), and the number of ongoing non-infectious complications, which was higher in the inpatient R/R group (33.3% vs. 3.6%, $p = .015$) (Table 2).

3.2 | The safety profile of outpatient VEN plus HMA treatment was acceptable with minimal TLS rate and no other limiting toxicities

One hundred and twenty-three AEs were documented during the study period, 116 of which were possibly related to VEN plus HMA treatment. AEs are summarized in Table S3.

Forty-two out of 59 (71.2%) patients experienced a grade III or IV AEs, with 83 total grade III or greater AEs. Among these 83 AEs, 24/83 (28.9%) showed a hematological etiology and 43/83 (51.8%) an infectious one. Globally, 21/59 (35.6%) patients experienced a hematological toxicity during treatment. Overall, the median platelet nadir was 8000/mm³ (range 3000–46 000/mm³) and the median hemoglobin value nadir was 7.2 g/dL (range 5.6–7.8 g/dL).

We evaluated the safety profile of the first 28 days of therapy in 19 patients (32.2%) who were hospitalized as compared with 40 patients who received the treatment in the outpatient setting. VEN dose escalation was managed with at least two weekly laboratory and clinical follow-ups, and only two patients (2/59, 3.4%) experienced a tumor lysis syndrome (TLS), both documented in the outpatient group. Of note, only 5 AEs were recorded during the ramp-up escalation VEN dose, 4/5 in the hospitalized patient group. Globally, 54 AEs were documented during cycle one in 36/59 (61%) patients, of whom 16/19 (84.2%) and 20/40 (50%) referred to inpatients or outpatients groups, respectively.

During the entire study period, 42/59 (71.2%) patients reduced VEN dose at least once (47 documented VEN dose reductions) due to AEs in the majority of cases (12/47 dose reductions, 25.5%).

Thirty-two out of 59 (54.2%) patients (43 withdrawals total) experienced at least one VEN withdrawal, caused by hematological AEs (15/43, 34.9%) and infectious AEs (20/43, 46.5%). Thirty-two out of 43 withdrawals (74.4%) had a median duration of 15 days (range 2–75, IQR: 9.5–28 days), whereas 11/43 (25.6%) resulted in a permanent discontinuation. The parameters evaluated for treatment suspension were each grade IV hematological AE (grade IV neutropenia in 5/15, grade IV pancytopenia in 8/15 and grade IV thrombocytopenia in 2/15 cases), excluding cases with persistent disease, and those occurring during the first cycle of therapy.

Twenty out of 43 VEN withdrawals occurred during the first cycle: Inpatient cases were likely to have a higher probability to suspend therapy due to treatment toxicity as compared to outpatient once (10/19 vs. 10/40, $p = .04$, IC: 0.91–12.26, OR: 3.26).

Finally, early 30-day and 60-day mortality was 2.5% (1/40) and 20% (8/40) versus 0% and 10.5% (2/19) in the outpatient and

TABLE 1 Patients' characteristics

Patients' characteristics	No. 59
Age at VEN therapy, median, years (min-max, IQR)	70.0 (22-88, IQR 63.5-78)
Sex, N (%)	
M	43 (72.9%)
F	16 (27.1%)
AML WHO type, N (%)	
<i>De novo</i>	34 (57.6%)
Secondary to MDS	13 (22.0%)
Secondary to MPN	9 (15.3%)
Therapy-related	3 (5.1%)
WBC at diagnosis, median, 10 ⁹ /L (min-max)	4.75 (0.9-212.0)
Risk stratification system ^(ELN17*) , N (%)	
Favorable	6 (10.2%)
Intermediate	28 (47.4%)
Adverse	22 (37.3%)
Not available	3 (5.1%)
ECOG performance status, N (%)	
0	17 (28.8%)
1	33 (55.9%)
2	9 (15.3%)
Hematologic parameters at VEN therapy	
Median WBC (N, IQR)	2.615/mmc (IQR 1.257-8.075)
Neutropenia grade III or greater, N (%)	33 (55.9%)
ANC (median, min-max)	800/mmc (100-8000)
Thrombocytopenia grade III or greater, N (%)	32 (54.2%)
Platelet count (median, min-max)	38.000/mmc (3.000-688.000)
Anemia grade III or greater, N (%)	26 (44.1%)
Hemoglobin level (median, min-max)	10.5 g/dL (5.8-11.6)
Previous HMA therapy, N (%)	27/59 (45.8%)
Previous infectious episodes	
Total, No.	39
Patients with at least one episode, N (%)	30 (50.1%)
Patients with ongoing antimicrobial therapy, N (%)	11/59 (18.6%)
First cycle, N (%)	
Inpatients	19 (32.2%)
Outpatients	40 (67.8%)

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; ELN, European Leukemia Net; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; VEN, Venetoclax; WBC, white blood cells; WHO, World Health Organization.

Sum of % may not be 100 due to rounding.

inpatient groups, respectively ($p = ns$). In all except one, the cause of death was the hematological disease progression (one patient died for a severe Sars-Cov2 pneumonia).

Taken together, these results indicate that the toxicity profile of VEN plus HMA in combination in the outpatient setting is similar to that observed for hospitalized patients.

3.3 | In the outpatient management of VEN and HMAs, an infectious prophylaxis inspired to intensive chemotherapy may reduce infections

Although infections prophylaxis is a major issue in AML patients, no standard of care has been fully defined in association with the VEN plus HMA regimen, particularly in the outpatient setting. According to institutional guidelines, which recommend an antimicrobial prophylaxis similar to what it is suggested for intensive chemotherapy, each patient developing a grade IV neutropenia received both antibacterial and antifungal prophylaxis. Antibiotic prophylaxis was given to 42/59 (71.2%) patients, consisting in the majority of the cases on Levofloxacin. Thirty-one over 40 (77.5%) outpatients and 11 over 19 (57.9%) hospitalized patients received antibiotic prophylaxis ($p = ns$, IC: 0.11-1.54, OR: 0.41). Antifungal prophylaxis was given to 46/59 (78%) patients, with no differences between out- and inpatient groups (31/40, 77.5% and 5/19, 26.3%, respectively; $p = ns$): posaconazole (30/46, 65.2%), fluconazole (11/46, 23.9%), isavuconazole (3/46, 6.5%), and voriconazole (2/46, 4.3%). In those patients, the VEN dose was adjusted according to current pharmacokinetics data.⁹ Among the two patient groups, posaconazole was given more frequently to the inpatient one (12/15, 80% vs. 18/31, 58.1%), while isavuconazole was prescribed only to hospitalized patients (3/15, 20%), and both fluconazole and voriconazole were given only to the outpatient group (11/31, 35.4% and 2/31, 6.5%, respectively). No significant differences in infectious prophylaxis were documented between patients receiving decitabine and those receiving azacytidine and between ND and R/R patients.

Twenty-seven patients experienced at least one infectious episode during treatment and 16 had a previous infectious clinical history (59.3%). Among these 16 patients, only 1/16 had an infectious episode after VEN and HMAs initiation caused by a pre-existing agent (febrile neutropenia with microbiologically documented *Klebsiella Pneumoniae* bacteremia). The median time to infection onset was 29 days (IQR: 19.25-86.25) from treatment initiation. While the rate of fungal infections was low and not significantly different between inpatient and outpatient group (2/19, 10.5% vs. 3/40, 7.5%), the number of patients who experienced at least one bacterial infection was lower among subjects treated in the outpatient setting (5/40, 12.5%) as compared to the hospitalized ones (12/19, 63.1%; $p < .0001$, IC: 2.72-56.17, OR: 11.33). Of note, over 18 febrile neutropenia episodes due to microbiologically documented bacteremia, 13 occurred in the hospitalized group, whereas only 5 in the outpatient one (13/19, 68.4%, vs. 5/40, 12.5%; $p < .0001$, IC:

TABLE 2 Comparison of patients' characteristics according to disease status and the inpatient versus outpatient setting

Potential confounders	Newly diagnosed				Relapsed/Refractory			p value
	IN (No. 4)	OUT (No. 12)	Total (No. 16)	p value	IN (No. 15)	OUT (No. 28)	Total (No. 43)	
Gender								
M	3 (75)	10 (83.4)	13 (81.3)	.607	11 (73.3)	19 (67.9)	30 (69.8)	.496
F	1 (25)	2 (16.6)	3 (18.8)		4 (26.7)	9 (32.1)	13 (30.2)	
ELN risk								
Low	1 (25)	2 (16.7)	3 (18.8)	.915	1 (11.1)	2 (7.1)	3 (7)	.522
Intermediate	1 (25)	4 (33.3)	5 (31.2)		6 (33.3)	17 (60.7)	23 (53.5)	
High	2 (50)	6 (50)	8 (50)		6 (33.3)	8 (28.6)	14 (32.4)	
NA	0 (0)	0 (0)	0 (0)		2 (22.2)	1 (3.6)	3 (7)	
Age (median)	72.5	79	79	.635	53	70	66	.001
ECOG PS scale								
0-1	2 (88.9)	11 (77.3)	13 (81.2)	.136	14 (93.3)	23 (82.1)	37 (86)	.304
>1	2 (11.1)	1 (22.7)	3 (18.8)		1 (6.7)	5 (17.9)	6 (14)	
Karnofsky score								
65%-100%	2 (50)	11 (91.7)	13 (81.3)	.136	14 (93.3)	23 (82.1)	37 (86)	.403
10%-65%	2 (50)	1 (8.3)	3 (18.7)		1 (6.7)	5 (17.9)	6 (14)	
HCT-CI score								
0-3	2 (50)	5 (41.7)	7 (43.8)	.608	12 (80)	21 (75)	33 (76.7)	.512
>3	2 (50)	7 (58.3)	9 (56.2)		3 (20)	7 (25)	10 (23.3)	
Disease status at VEN								
First-line rescue	/	/	/	/	7 (46.7)	13 (46.4)	20 (46.4)	.163
First relapse					2 (13.3)	10 (35.7)	12 (27.8)	
≥2 relapse					6 (40)	5 (17.9)	11 (25.8)	
Previous allo-HSCT								
Yes	/	/	/	/	3 (20)	5 (17.9)	8 (18.6)	.583
No					12 (80)	23 (82.1)	35 (81.4)	
WBC at VEN (median)	13.120	4360	4360	.608	1930	2515	2305	.235
ANC at VEN (median)	1950	625	930	.569	455	700	600	.208
Platelet count (median)	31.000	91.500	64.000	.077	21.000	37.000	24.000	.744
Infections pre-VEN therapy								
Yes	1 (25)	0 (0)	1 (6.3)	.250	12 (80)	17 (60.7)	29 (67.4)	.173
No	3 (75)	12 (100)	15 (93.7)		3 (20)	11 (39.3)	14 (32.6)	
Ongoing infections at VEN therapy								
Yes	0 (0)	0 (0)	0 (0)	/	2 (13.3)	0 (0)	2 (4.7)	.116
No	4 (100)	12 (100)	16 (100)		13 (86.7)	28 (100)	41 (95.3)	
Patients with ongoing antimicrobial therapy at VEN therapy								
Yes	2 (50)	0 (0)	2 (12.5)	.050	9 (60)	1 (3.6)	10 (23.3)	.001
No	2 (50)	12 (100)	14 (87.5)		6 (40)	27 (96.4)	33 (76.7)	
Others ongoing complications at VEN therapy								
Yes	1 (25)	0 (0)	1 (6.3)	.250	5 (33.3)	1 (3.6)	6 (13.9)	.015
No	3 (75)	12 (100)	15 (93.7)		10 (66.7)	27 (96.4)	37 (86.1)	

Note: IN: first 28-day cycle of therapy as inpatients, with a planned hospitalization.

Abbreviations: allo-HSCT, allogeneic-HSCT; AML, acute myeloid leukemia; ANC, absolute neutrophil count (n^o/mmc); ECOG PS scale, Eastern Cooperative Oncology Group Performance Status Scale; ELN, European Leukemia Net; HCT-CI score, Hematopoietic Cell Transplantation-specific Comorbidity Index score; OUT, onset treatment within an outpatient plan; VEN, Venetoclax; WBC, white blood Cells.

Sum of % may not be 100 due to rounding.



3.35–73.03.74, OR: 14.20). Overall, 23 cases of documented bacterial AEs were documented in our study population, which occurred in the outpatient group only in 5 patients (21.7%), while hospitalized subjects developed more bacterial infections per person ($p = .0003$).

These data suggest that intensive antimicrobial prophylaxis is associated with an acceptable rate of infections in patients receiving VEN plus HMAs in the outpatient setting, with a bacterial infection rate significantly reduced in comparison with hospitalized patients.

3.4 | No planned admission to hospital reduced overall time of hospitalization in patients receiving VEN + HMAs

Among the 19 inpatient cases, the median duration of the hospitalization was 32 days (range 10–68 days). Since hospitalizations might occur as AEs consequence, we analyzed the rate of (re)admission in the two groups. Overall, 23/59 (38.9%) patients were (re)hospitalized for AEs/treatment complications at least once: 8/16 (50%) ND and 15/43 (34.9%) R/R cases. Microbiologically documented febrile neutropenia (7/23) and pneumonia (8/23) were the two main AEs requiring hospitalization with no significant differences between patients treated in an outpatient setting and those hospitalized for the first cycle. In details, 36.8% of inpatient group and 40% of outpatient one needed to be (re)admitted to the hematology unit while the combo therapy was given domiciliary ($p = ns$). Importantly, among the outpatient group, only 6/40 (15%) were hospitalized during the first 28 days of treatment. Based on these data, the mean time of hospitalization, which included planned hospitalization for those patients who received the first cycle as inpatients added to the hospitalization time due to complications, was significantly inferior in the outpatient group as compared to the inpatient one (5.9 vs. 39.7 days, $p < .0001$; Figure 1A), and also considering only patients with at least 100 days of follow-up, the difference between the two groups was still significant (7.8 vs. 40.9 days, $p < .0001$; Figure 1B). The average hospitalization time for AEs management was comparable between the two cohorts (5.9 vs. 6.0 days, $p = ns$, for in and outpatients, respectively; Figure 1C).

These data suggest that an outpatient management of VEN plus HMAs may reduce the global duration of hospitalization.

3.5 | Total outpatient management of VEN and HMA combination did not significantly impact on treatment effectiveness

The overall response (OR) was classified as complete response (CR), complete response with incomplete hematologic recovery (CRi), partial remission (PR), hematological improvement (HI), and stable disease (SD), as summarized in Table 3.

In ND AML patients ($n = 16$), the OR Rate (ORR) to VEN plus HMAs, defined as CR plus CRi plus HI, was 62.5% (10/16), with a median follow-up of 117 days (IQR: 92–173.75): 2 HIs, 6 CRs, and 2

CRi. Thus, the CR/CRi rate was 50% (8/16). The median time to first response was 38 days (IQR: 29.75–62) with a median of 1.4 cycles to response. Two responding patients relapsed (20%), with a median duration of response (DOR) of 7.8 months. Median overall survival (OS) was 247 days (95% CI: 177.71–316.58; Figure 2A). Of note, ORR in the outpatients group compared with the inpatient one was similar (8/12, 66.7% vs. 2/4, 50%). Moreover, no significant difference in OS between the two groups was observed (Log Rank Mantel-Cox $p = .876$; Figure 2B).

In R/R AML patients ($n = 43$), with a median follow-up of 173 days (IQR: 74–339), the ORR was 41.8% (18/43): 7 HIs, 9 CRs, and 2 CRi, with a CR/CRi rate of 25.6% (11/43). The median time to first response was 66.5 days (IQR: 36–96.75), with a median of 2.4 cycles to response. Fifteen patients (83.3%) relapsed with a median DOR of 4.36 months. Nine out of 43 (20.9%) R/R patients received a subsequent allo-HSCT. Median OS was 219 days (95% CI: 91.8–346.2; Figure 3A). As previously reported for ND patients, ORR was similar between inpatient and outpatient groups (6/15, 40% vs. 12/28, 42.8%) with no significant difference in OS (Log Rank Mantel-Cox $p = .734$; Figure 3B).

These data suggest that the *ab initio* outpatient management of VEN plus HMAs might not impact on the treatment effectiveness.

4 | DISCUSSION

In this real-world retrospective study, we evaluated the feasibility and the impact on effectiveness of an outpatient management of VEN plus HMA therapy for AML patients with active disease respect with an inpatient initial management (first cycle). Toxicity profile and infection rate were low in the outpatient group, with a global reduction in the time of hospitalization and a treatment effectiveness similar to what reported in clinical trials and not influenced by the use of an outpatient management.

Venetoclax and HMA administration to elderly and/or unfit-to-chemotherapy AML patients in the real-life setting is rapidly increasing as the standard of care due to the favorable results obtained in clinical trials as the first-line therapeutic option.^{3,4,12,13} However, some important questions regarding its management are still open. In particular, it is not fully established whether the VEN and HMA combination therapy requires upfront hospitalization during the first cycle, as recently suggested by a panel of experts,¹⁴ or, conversely, may be assimilated to the use of hypomethylating drugs, which are safely given within a total outpatient plan.^{15–18} Although very few cases of TLS after VEN and HMAs in AML have been reported,^{3,4,13} TLS represents the major concern in administering the combination outside a hematology unit, given the occurrence of fatal TLS events in CLL patients treated with VEN.¹⁹ Our retrospective analysis showed that only 5 AEs were recorded during the ramp-up phase of the drug, which appeared globally safe. Notably, those patients who received the first cycle out of hospital did not show higher incidence of AEs as compared to those who were treated in hospital. Along with a careful evaluation of each single case, these data suggest that

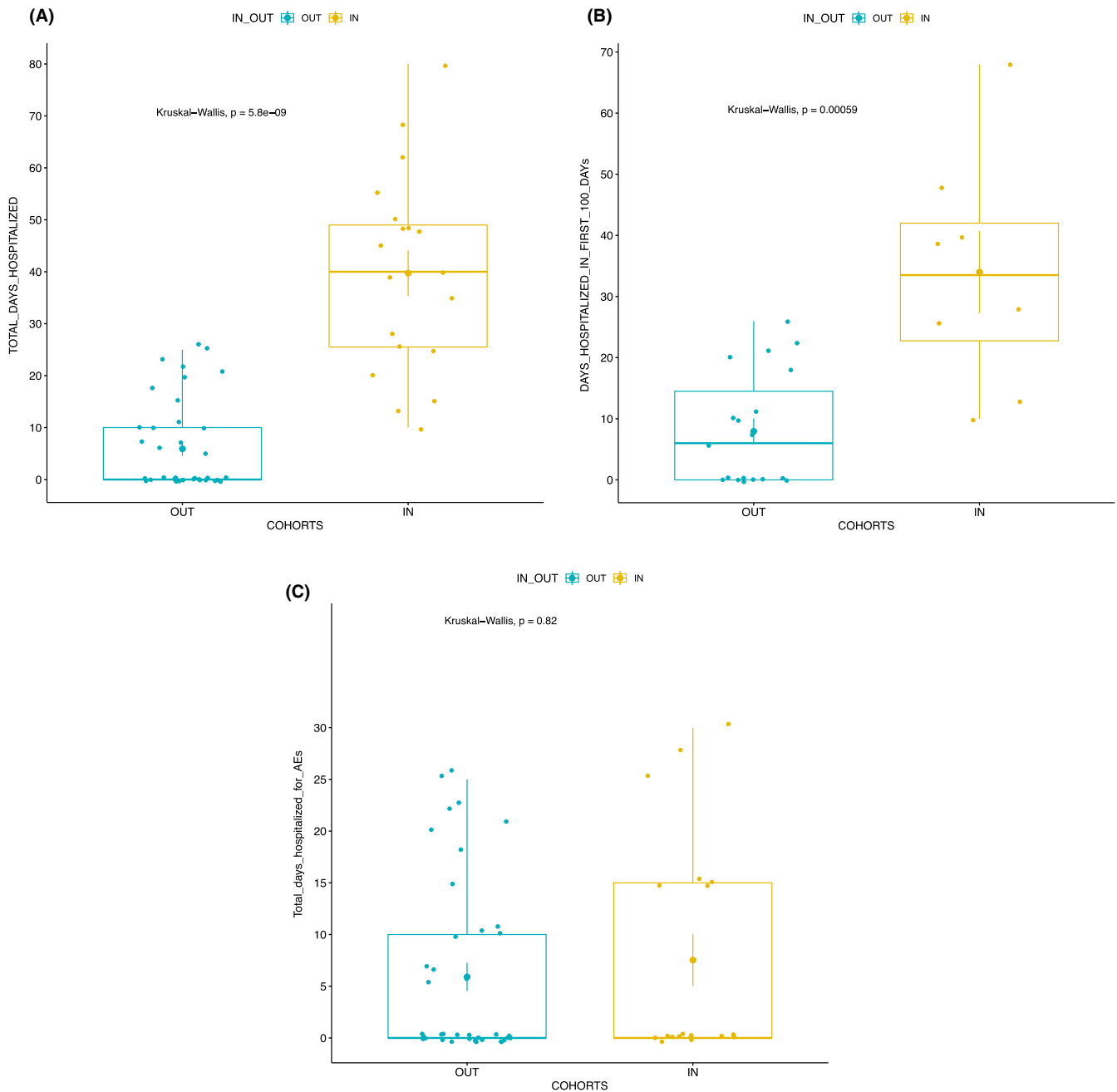


FIGURE 1 Difference in median time of hospitalization in the inpatient and outpatient groups: (A) overall; (B) in patients with, at least, 100 days of follow-up; (C) due to AEs management

TLS and AEs associated with ramp-up phase may not represent a major concern and revealed that an outpatient management is feasible and safe.

Antimicrobial prophylaxis is standard of care in hospitalized AML patients receiving intensive chemotherapy.^{20,21} On the contrary, the most appropriate anti-infectious prophylaxis for AML patients treated out of hospital is a major area of investigation, where no clear and settled guidelines have been established. The infection risk in elderly AML patients undergoing HMA therapy in outpatient setting has not been quantified and is heterogeneously documented.²² In this scenario, partly due to the well-known VEN pharmacological

interaction, the indication for antimicrobial prophylaxis, especially antifungal one, is even more controversial. The overall risk of invasive fungal infections (IFIs) during HMAs therapy is considered low, but the addition of VEN has been recently reported to increase the fungal risk.^{13,23–25} In early clinical trials with the combo therapy (VEN plus HMAs),¹³ azoles were prohibited due to a negative drug–drug interaction with VEN through CYP3A4. Further recommendations have suggested the need for a VEN dose adjustment when given with azoles (overall voriconazole and posaconazole), but the clinical efficacy of the reduced dosage of VEN is still uncertain. In our cohorts of ND and R/R AML patients treated with VEN plus HMAs

TABLE 3 Responses to VEN plus HMA treatment

Treatment Effectiveness (Response to VEN and HMAs)	ND patients (No. 16)		R/R patients (No. 43)	
	IN (No. 4)	OUT (No. 12)	IN (No. 15)	OUT (No. 28)
Response status at 2 months of therapy, evaluable N (%)	3/4 (75%)	8/12 (66.7%)	11/15 (73.3%)	19/28 (67.8%)
SD	1/4 (25%)	-	3/15 (20%)	10/28 (35.7%)
PR	-	1/12 (8.3%)	1/15 (6.7%)	1/28 (3.6%)
HI	-	2/12 (16.7%)	3/15 (20%)	4/28 (14.3%)
CRi	1/4 (25%)	1/12 (8.3%)	-	1/28 (3.6%)
CR	1/4 (25%)	4/12 (33.3%)	3/15 (20%)	3/28 (10.7%)
DP	-	-	1/15 (6.7%)	-
Response status at 4 months of therapy, evaluable N (%)	1/4 (25%)	4/12 (33.3%)	7/15 (46.7%)	17/28 (60.7%)
SD	-	-	1/15 (6.7%)	7/28 (25%)
HI	-	1/12 (8.3%)	-	5/28 (17.8%)
CRi	-	-	-	1/28 (3.6%)
CR	1/4 (25%)	3/12 (25%)	6/15 (40%)	3/28 (10.7%)
Relapse	-	-	-	1/28 (3.6%)
Overall response rate censored to HSCT, N (%)	2/4 (50%)	8/12 (66.7%)	6/15 (40%)	12/28 (42.8%)
HI	-	2/12 (16.7%)	1/15 (6.7%)	6/28 (21.4%)
CRi	1/4 (25%)	1/12 (8.3%)	-	2/28 (7.1%)
CR	1/4 (25%)	5/12 (41.7%)	5/15 (33.3%)	4/28 (14.3%)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DP, disease progression; HI, hematologic improvement; HMAs, hypomethylating agents; HSCT, hematopoietic stem cell transplant; ND, newly diagnosed; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VEN, Venetoclax.

Sum of % may not be 100 due to rounding.

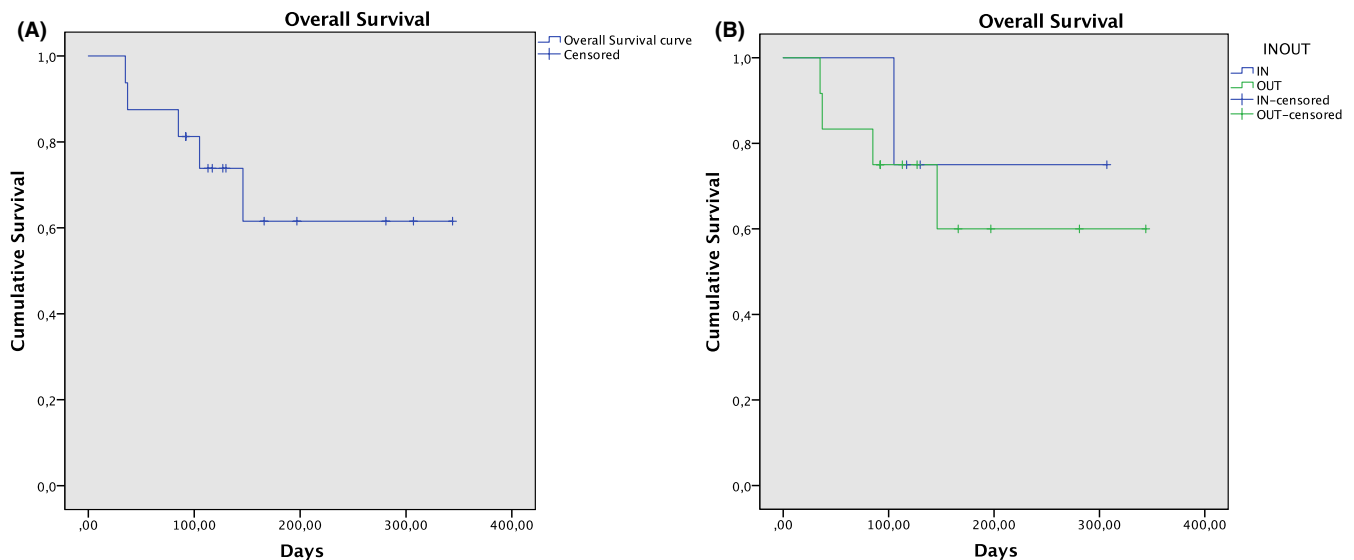


FIGURE 2 Newly diagnosed AML patients: (A) Overall Survival after VEN plus HMA; (B) differences in Overall Survival between the Outpatient and Inpatient group

within a total outpatient management, an antimicrobial prophylaxis, including antifungal agents, was considered necessary during severe neutropenia due to a local significant rate of IFIs in hematology and

was mostly based on the recommendation established for intensive chemotherapy. Posaconazole, which is approved for neutropenia following intensive induction or rescue chemotherapy and allo-HSCT,

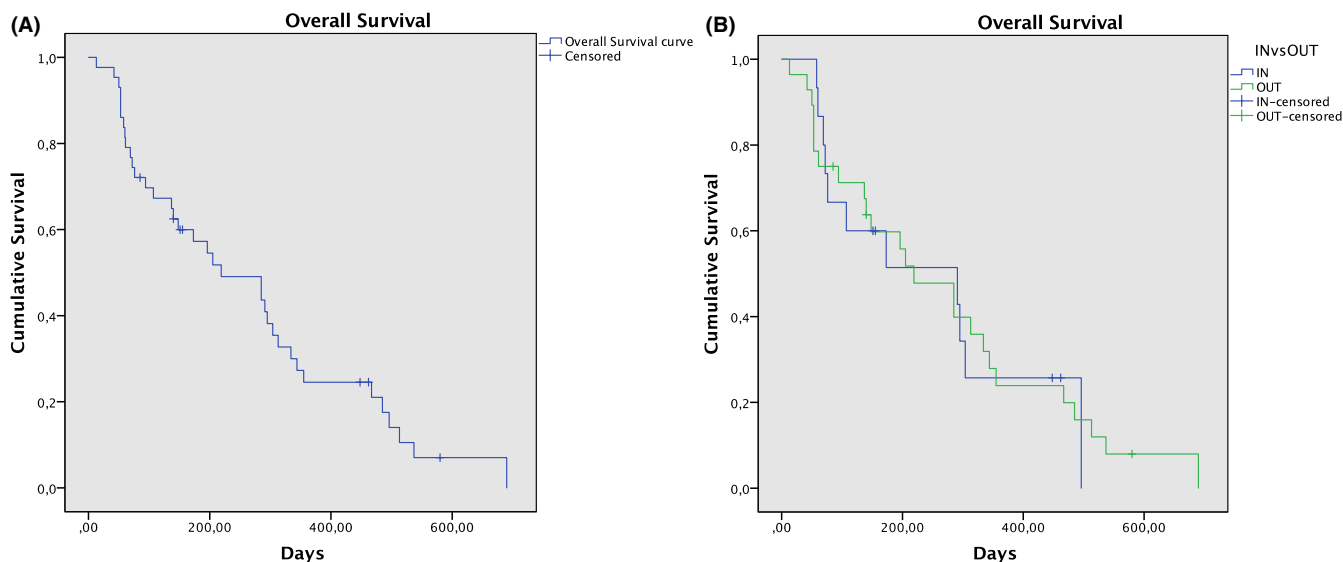


FIGURE 3 Relapsed/Refractory AML patients: (A) Overall Survival after VEN plus HMAs; (B) differences in Overall Survival between the Outpatient and Inpatient group

was extensively administered in our cohort (65.2%), in comparison with the 26.6% previously reported in a study addressing the risk of IFIs with this regimen.²⁶ This approach seemed to be effective in preventing IFIs considering a fungal rate of 8.5%, significantly lower than that reported in a similar population of R/R AML patients.²⁵ These results are consistent with those obtained from investigational studies on early discharge after intensive chemotherapy^{27,28} or on the total outpatient management during induction chemotherapy.⁸ Of note, febrile neutropenia episodes due to microbiologically documented bacteremia were significantly reduced in patients who received the first cycle of combo therapy as outpatients. Since the same antibiotic prophylaxis was adopted for in- and outpatients, while not excluding other factors, our data may suggest that a total outpatient management may reduce the exposure of patients to nosocomial bacterial infections which present a high rate of multi-drug resistance, thus resulting in a global advantage in terms of infection rate and infection severity.

In our study, VEN and HMA regimen was mostly initiated in the outpatient setting, avoiding initial hospitalization, which was prolonged in the inpatient group with a median duration of 32 days. A therapeutic strategy with no planned admission to hospital has been reported to improve patients' QoL⁶ as well as compliance and adherence to therapy. Importantly, such strategy is also associated with higher widespread therapy availability and reduced infections-related healthcare costs.⁵⁻⁷ Therefore, a total outpatient management of VEN and HMA may improve not only patients' QoL, but may also represent a significant pharmacoeconomic and healthcare management benefit. Indeed, our data revealed that patients who received out-of-hospital treatment have a significantly reduced overall time of hospitalization, with a potential benefit in the global economic burden associated with VEN plus HMA treatment. It should be emphasized that the total outpatient management of these frail patients requires an intensification of usual monitoring by increasing

the frequency of medical examinations and laboratory tests. For that, a specialized and trained team of nurses and physicians operating in the outpatient setting is mandatory. This work may provide the preliminary background for defining operative criteria to assign a patient candidate to VEN and HMAs therapy to an out- or inpatient management.

Results from clinical trials are not always reproducible in a real-life setting. Regarding HMA, some studies reported lower survival outcomes with azacytidine in a real-life setting in comparison with clinical trials in AML, MDS, and chronic myelomonocytic leukemia patients.²⁹⁻³¹ Combined VEN and HMA therapy was only recently approved, and few data are available to compare clinical trials with real-life clinical practice. One recent study reported that ND AML patients treated with VEN and azacytidine in a "real-world" scenario had inferior outcomes.²⁴ To the best of our knowledge, no data are available about the impact of a total outpatient management on the effectiveness of VEN plus HMAs treatment in a real-life setting and outside clinical trials. With the limitations of a retrospective and single-center study, our data highlight the safety profile and feasibility of a total outpatient management of VEN and HMAs treatment. In our study, overall efficacy data are in line with those collected from similar series of ND and R/R AML patients, who received the combination within and outside clinical trials.^{25,32-35} Importantly, total outpatient management did not negatively impact on treatment effectiveness both in ND and R/R patients.

5 | CONCLUSIONS

With the limitations of a single-center retrospective study, our study highlights the safety and feasibility of a total outpatient administration of VEN plus HMAs in a real-life setting. Total out-of-hospital management of this therapy, for which a strict patients monitoring



is required, may ameliorate patients' quality of life, yield pharmacoeconomic benefits, and allow its widespread availability and, thus, should be encouraged. Further studies addressing the global impact of such approach on larger cohorts of AML patients receiving VEN and HMAs therapy are highly warranted.

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CONFLICT OF INTEREST

Dr. Cristina Papayannidis received honoraria from Pfizer, Amgen, and Novartis. Dr. Antonio Curti received honoraria from Novartis, Pfizer, and Abbvie and acted as speaker in Advisory Board for Novartis and Abbvie. Prof. Michele Cavo acted as consultant for and received honoraria from AbbVie, Glaxo Smith Kline, Bristol-Myers Squibb, Adaptive Biotechnologies, Takeda, Janssen, Celgene, and Amgen. Moreover, Prof. Cavo is in the speaker's bureau of AbbVie and Glaxo Smith Kline. The other authors declare no conflict of interest or activities that could appear to have influenced this manuscript.

AUTHOR CONTRIBUTIONS

C.P., A.C. and J.N. involved in conceptualization. G.C., G.M. and R.S. involved in methodology. A.C., N.T. and E.O. involved in validation. C.P., J.N. and A.C. involved in formal analysis. E.O., L.B., N.T., A.C., C.P., G.C., G.M., C.S., S.P., P.R., C. D., C.B., L.Z., R.A., M.S., S.P. and J.N. involved in investigation. M.C., A.C., C.P. and S.P. involved in resources. J.N., G.C., G.M., V.S., M.S. and R.S. involved in data curation. J.N. and C.P. involved in writing—original draft preparation. A.C., C.P. and J.N. writing—review and editing. A.C. and M.C. involved in supervision. A.C. and M.C. involved in project administration. M.C. and A.C. involved in funding acquisition.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki.

INFORMED CONSENT STATEMENT

Data were collected in accordance with Good Clinical Practice, and all participants signed a written informed consent.

DATA AVAILABILITY STATEMENT

The dataset (individual raw data) is available upon request.

REFERENCES

- Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152.
- DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135(2):85-96.
- DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
- 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(24):2137-2145.
- Efficace F, Kemmler G, Vignetti M, Mandelli F, Molica S, Holzner B. Health-related Quality of Life Assessment and reported outcomes in leukaemia randomised controlled trials - a systematic review to evaluate the added value in supporting clinical decision making. *Eur J Cancer*. 2008;44(11):1497-1506.
- Møller T, Adamsen L, Appel C, et al. Health related quality of life and impact of infectious comorbidity in outpatient management of patients with acute leukemia. *Leuk Lymphoma*. 2012;53(10):1896-1904. doi:10.3109/10428194.2012.676169
- Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8(5):R291-R298.
- Mabrey FL, Gardner KM, Dorcy KS, et al. Outpatient intensive induction chemotherapy for acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood Adv*. 2020;4(4):611-616.
- Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-positaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Ther*. 2017;39(2):359-367.
- 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(4):424-447.
- National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE).v.5.0. Cancer Ther Eval Progr [Internet]. 1999;183. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed November 27, 2017.
- Wei AH, Strickland SA, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019;37(15):1277-1284.
- DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.
- Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia* [Internet]. 2019;33(12):2795-2804. doi:10.1038/s41375-019-0612-8
- Malik P, Cashen AF. Decitabine in the treatment of acute myeloid leukemia in elderly patients. *Cancer Manag Res*. 2014;6(1):53-61.
- Crujisen M, Lübbert M, Wijermans P, Huls G. Clinical results of hypomethylating agents in AML treatment. *J Clin Med*. 2014;4(1):1-17.
- Tawfik B, Sliesoraitis S, Lyerly S, et al. Efficacy of the hypomethylating agents as frontline, salvage, or consolidation therapy in adults with acute myeloid leukemia (AML). *Ann Hematol*. 2014;93(1):47-55.
- Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299. doi:10.1182/blood-2015-01-621664
- Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.
- De Rosa FG, Motta I, Audisio E, et al. Epidemiology of bloodstream infections in patients with acute myeloid leukemia undergoing levofloxacin prophylaxis. *BMC Infect Dis*. 2013;13(1).
- Mellinghoff SC, Panse J, Alalok N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Ann Hematol*. 2018;97(2):197-207.



22. Pagano L, Busca A, Candoni A, et al. Risk of infection in elderly patients with AML and MDS treated with hypomethylating agents. *Acta Biomed.* 2018;89(11-S):5-39. doi:[10.23750/abm.v89i11-S.7988](https://doi.org/10.23750/abm.v89i11-S.7988)
23. Pomares H, Arnan M, Sánchez-Ortega I, Sureda A, Duarte RF. Invasive fungal infections in AML/MDS patients treated with azacitidine: a risk worth considering antifungal prophylaxis? *Mycoses.* 2016;59(8):516-519.
24. 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(20):2911-2919.
25. 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(3):401-407.
26. Aldoss I, Dadwal S, Zhang J, et al. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. *Blood Adv.* 2019;3(23):4043-4049.
27. Walter RB, Lee SJ, Gardner KM, et al. Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study. *Haematologica.* 2011;96(6):914-917.
28. Walter RB, Taylor LR, Gardner KM, Shannon Dorcy K, Vaughn JE, Estey EH. Outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia. *Clin Adv Hematol Oncol.* 2013;11(9):571-577.
29. Helbig G, Chromik K, Woźniczka K, et al. Real life data on efficacy and safety of azacitidine therapy for myelodysplastic syndrome, chronic myelomonocytic leukemia and acute myeloid leukemia. *Pathol Oncol Res.* 2019;25(3):1175-1180.
30. Zeidan AM, Davidoff AJ, Long JB, et al. Comparative clinical effectiveness of azacitidine versus decitabine in older patients with myelodysplastic syndromes. *Br J Haematol.* 2016;175(5):829-840.
31. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232. doi:[10.1016/s1470-2045\(09\)70003-8](https://doi.org/10.1016/s1470-2045(09)70003-8)
32. Al-kali A, Begna K, Elliott M, Hogan W. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. *Am J Hematol.* 2020;95(12):1511-1521.
33. Gaut D, Burkenroad A, Duong T, Feammelli J, Sasine J, Schiller G. Venetoclax combination therapy in relapsed/refractory acute myeloid leukemia: a single institution experience. *Leuk Res.* 2020;90(90):106314.
34. Bewersdorf JP, Giri S, Wang R, et al. Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis. *Haematologica.* 2020;105(5):2659-2663.
35. Aldoss I, Dongyun Yang AA, Ali H, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia Venetoclax. *Haematologica.* 2018;15:404-407.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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