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Real-life data of azacitidine-venetoclax combination in acute myeloid leukemia patients: a single center experience

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ABSTRACT

Aims: To evaluate real-life data on the efficacy and safety of Venetoclax (Ven) therapy used in combination with hypomethylating agent (HMA) in patients with acute myeloid leukemia (AML).

Methods: The records of newly diagnosed, relapsed or refractory (RR) AML patients over 18 years of age who were planned to be treated with Azacitidine (AZA) combined with Ven because they were not suitable for intensive chemotherapy and patients who received AZA combined with Ven maintenance therapy after achieving remission were retrospectively analyzed. The standard protocol for patients is subcutaneous or intravenous AZA 75 mg/m2 on days 1-7/ every 28 days + oral Ven treatment 100-400 mg/day for 28 days. The treatment response rates, survival times, and side effect profiles of 18 newly diagnosed patients, 12 RR patients, and 4 patients receiving AZA+Ven as maintenance treatment between January 2021 and March 2022 were evaluated.

Results: It was found that 8 of the 34 patients (23.5%) who were examined in the present study died before the first response could be evaluated. When the response rates were evaluated, complete response (CR) or complete remission with incomplete blood count recovery (CRi) (CR+CRi) was found to be 61% in the group receiving AZA+Ven in the first line, and CR+CRi was 50% in the group receiving AZA+Ven because of RR AML. In the group receiving AZA+Ven in the first line, the average Overall Survival (OS) was 8.00 months (95% CI: 1.58-14.41), and 7.00 months in the RR group (95% CI: 1.78-12, 21). All patients in the group receiving AZA+Ven for maintenance purposes were alive and the median follow-up period was 12.50±6.02 months in this group (Mean±SD). The most common side effect was neutropenia, and the most common cause of death was disease progression.

Conclusion: In AML patients ineligible for intensive treatment due to advanced age or comorbidities, real-life data of AZA+Ven therapy with effective CR+CRi rates and a manageable spectrum of side effects promise hope.

Keywords: Acute myeloid leukemia, azacitidine, hypomethylating agent, venetoclax

INTRODUCTION

Targeted agents act specifcally in regions that are overexpressed in cancer cells, thereby they increase the effectiveness of antineoplastic therapy and significantly reduces the adverse effects (AEs), presented by conventional chemotherapy.[1] As one of the targeted treatments, Ven is an oral, highly selective inhibitor used against B-cell lymphoma 2 (BCL-2), which is an antiapoptotic protein and directs cells to apoptosis. Its use in acute myeloid leukemia (AML) has come to the agenda because BCL-2 is overexpressed in the leukemic stem cell population.[2] The incidence of AML, which is the most common type of acute leukemia in adults, is 3.5/100.000 per year.[3]

Since the median age at the time of AML diagnosis is 68, and a significant rate of patients are not suitable for intensive treatment because of accompanying comorbidities and low physical performance, fragile AML patients have been treated with HMA because of its tolerability and relatively safe profile for many years. The rates of complete remission with HMA alone are approximately 25-30% and the median OS is approximately 10 months.[4] Response with HMAs is achieved in a median of 3-4 months, however, only 2%-4% of patients aged ≥60 years who cannot undergo stem cell transplantation can maintain their disease-free status for 10 years after their treatment.[5]

Although a rapid response was achieved in monotherapy studies on Ven in AML, the fact that response rates were not permanent and that higher response rates were obtained in the group previously received HMA led to a tendency towards combination therapies.[6]

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The aim of this study was to evaluate real-life outcomes regarding efficacy and safety by analyzing the data of patients who received HMA-combined Ven therapy because they were not eligible for intensive chemotherapy and to compare them with the data obtained in clinical trials.

METHODS

The study was granted ethical approval by the University of Health Sciences Gülhane Scientific Researches Ethics Committee (Date: 27.06.2022, Decision No: 2022-249). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The file records of the patients who were followed up with a diagnosis of AML in the Adult Hematology Clinic of Gülhane Training and Research Hospital and received combined Ven treatment with AZA between January 2021 and March 2022 because they were not suitable for intensive chemotherapy were examined retrospectively. Those who received combined treatment in the first line, those who received treatment for RR AML, and those who received as AML maintenance treatment after achieving remission were assessed separately.

Responses were evaluated per the International Working Group criteria for AML. CR designation requires that the patient achieve the morphologic leukemia-free state and have an absolute neutrophil count (ANC) more than 1,000/L, platelets (plt) more than 100,000/L and the bone marrow would have less than 5% blasts and no Auer rods. For the definition of CRi, all other criteria must be met of CR except ANC >1,000/L or plt count >100,000/L. Partial remission (PR) designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.[7] Efficacy was assessed as rate of objective response (CR + CRi + PR). Duration of response (DOR) for patients who achieved a CR or CRi and OS was evaluated. Investigator-assessed adverse events (AEs) were summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 6.0.[8]

Sattistical Analysis

Statistical analyses were made by using the IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). The descriptive statistics were presented as n and % for categorical variables and as Mean±SD or Median (Min-Max) for continuous variables. The Wilcoxon Test, which is one of the nonparametric tests, was used for before and after comparisons of some numerical parameters. The Kruskal Wallis Test, which is one of the nonparametric tests, was used for triple comparisons. The Bonferroni Test was used as the post-hoc test. Finally, the Kaplan-Meier method was used to determine the survival durations, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 34 patients were evaluated in the study, including 18 newly diagnosed patients, 12 RR patients, and 4 patients receiving AZA+Ven as maintenance treatment. Aside from age, these patients had very fragile characteristics because of accompanying comorbidities, and 28 out of 34 patients (82.3%) had at least 1 chronic disease (diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, congestive heart failure, cerebrovascular disease, bullous pemphigoid, sarcoidosis, asthma, cholelithiasis, hypothyroidism, osteomyelitis) and the presence of a hip prosthesis was noted in 1 patient. Also, as well as these chronic diseases, 1 patient had a history of breast cancer, 1 had prostate cancer, 1 larynx cancer, 1 sarcoma, and 1 non-hodgkin lymphoma (NHL), and 1 patient had a history of lung cancer together with the diagnosis of AML. Baseline demographic and clinical characteristics of the patients are given in **Table 1**.

Two patients who received AZA+Ven in the 1st line and whose progression status was stated as "undetermined" were reported in this way because they died before the response evaluation could be made during the 2nd cycle (cause of death was determined as febrile neutropenia (FEN) in 1 patient and COVID-19 in the other). 5 patients in RR group whose progression status was stated as "undetermined" were clinically and laboratory compatible with progression but they were recorded in this way because bone marrow (BM) examination was not performed to reveal progression. Following the AZA+Ven treatment, 1 out of 12 patients (8.3%) in the RR group and 1 out of 4 patients (25%) in the maintenance group underwent Allogeneic stem cell transplantation (ASCT).

ANC, hemoglobin (Hb), and plt values that were monitored after initiation of AZA+Ven treatment were found to be lower in the 3 groups when compared to the values before treatment. Although the decrease in all 3 series was statistically significant in the first line and RR groups ($p<0.001$), these values were not statistically significant in the maintenance group ($p>0.05$).

The grades of cytopenias are more important rather than the occurrence of cytopenias. The degrees of cytopenia under AZA+Ven were determined as follows.

Grade 3-4 thrombocytopenia was 77.8%/75%/50% in the first line/RR and maintenance groups, respectively.

Grade 3-4 neutropenia was 66.7%/75%/100% in the first line/RR and maintenance groups, respectively.

Grade 3-4 anemia was 44.5%/58.3%/25% in the first line/RR and maintenance groups, respectively.

Rapid apoptosis occurs and leukemic cells are rapidly removed from the BM after AZA+Ven treatment. BM blast rates before starting AZA+Ven, number of cycles completed before response evaluation, and BM blast rates after the treatment are given in **Table 2**.

Table 1: Baseline demographic and clinical characteristics of the patients

	First Line (n=18)
Age: Median (min-max)	77 (43-89)
Gender: F/M (n/%)	6/12 (33.3/66.7)
ECOG PS: 1/2/3/4 (n/%)	1/9/6/2 (5.6/50/33.3/11.1)
AML type:De-Novo /Seconder (n/%)	11/7 (61.1/38.9)
MDS history: Yes/No (n/%)	3/15 (83.3/16.7)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/14/4 (0/77.8/22.2)
Median total number of Ven cycles: (min-max)	3.0 (1-15)
Relapse /Progression: Yes/No/Undetermined (n/%)	4/12/2 (22.2/66.7/11.1)
Median time to Relapse/Progression: month (min-max)	7.0 (6.0-12.0)
Median follow-up:month (min-max)	5.0 (1.0-19.0)
Alive / Exitus (n/%)	6/12 (33.3/66.7)
RR (n=12)	
Age: Median (min-max)	62 (25-79)
Gender: F/M (n/%)	5/7 (41.7/58.3)
ECOG PS: 1/2/3/4 (n/%)	4/5/3/0 (33.3/41.7/25/0)
AML type:De-Novo /Seconder (n/%)	8/4 (66.7/33.3)
MDS history: Yes/No (n/%)	2/10 (16.7/83.3)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/8/2 (0/80/20)
Median number of treatment lines prior AZA+Ven:(min-max)	3.0 (1.0-6.0)
Median DOR maintained with last treatment prior AZA+Ven:month (min-max)	8.5 (2.0-28.0)
Prior hypomethylating agent, Yes/No (n/%)	10/2 (83.3/16.7)
Median total number of Ven cycles: (min-max)	2.5 (1.0-14.0)
Relapse /Progression: Yes/No/Undetermined (n/%)	4/2/5 (33.3/25/41.7)
Median time to Relapse/Progression (min-max)	6.0 (1.0-10.0)
Median follow-up:month (min-max)	2.0 (1.0-15.0)
Alive / Exitus (n/%)	3/9 (25/75)
Maintenance (n=4)	
Age: Median (min-max)	44 (31-61)
Gender: F/M (n / %)	2/2 (50/50)
ECOG PS: 1/2/3/4 (n/%)	3/1/0/0 (75/25/0/0)
AML type:De-Novo /Seconder (n / %)	3/1 (75/25)
MDS history: Yes/No (n/%)	1/3 (25/75)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/3/1 (0/75/25)
Median total number of Ven cycles: (min-max)	8.5 (2-19)
Relapse /Progression: Yes/No/Undetermined (n/%)	0/40 (0/100/0)
Median follow-up:month (min-max)	12.5 (6.0-19.0)
Alive / Exitus (n/%)	4/0 (100/0)

F:Female. M:Male. DOR:Duration of Remission AML:Acute Myeloid Leukemia, Fav:Favorable Int:Intermediate Adv:Adverse MDS: Myelodysplastic Syndrome, ECOG PS:Eastern Cooperative Oncology Group Performance Score, Genetic risk classification is based on the European Leukemia Network (ELN) 2022 criteria

Table 2. Bone marrow results before/after AZA+Ven

	First Line (Mean±SD)	RR (Mean±SD)	Maintenance (Mean±SD)
Number of Ven cycles prior to 1st BM assessment (n)	2.14±1.51	2.62±2.06	2.00±1.00
Number of Ven cycles prior to 2nd BM assessment (n)	4.83±2.92	9.00±1.41	2.00±
Number of Ven cycles prior to 3rd BM assessment (n)	5.50±2.12	-	-
BM blast rate prior Ven (%)	57.27±21.37	58.90±22.24	1.50±0.88
BM blast at the 1st assessment after Ven (%)	9.50±15.04	31.12±34.39	0.66±0.57
BM blast at the 2nd assessment after Ven (%)	6.66±9.22	11.00±12.72	-
BM blast at the 3rd assessment after Ven (%)	16.00±19.79	-	-

Ven:Venetoclax. BM:Bone Marrow

In the present study, 4 of 18 patients (22.2%) who received AZA + Ven in the first line and 4 of 12 patients (33.3%) who received AZA + Ven for RR AML died before the first response evaluations. Although it seems that sufficient blast clearance was not achieved in the BM examinations performed for 1st response evaluation (Table 2), when the sub-analyses were examined, remission was achieved in 10 out of 14 patients (71.4%) in first-line group and in 3 out of 8 patients (37.5%) in the RR group . Despite the high remission rates obtained in the 1st response evaluation, the reason for the high mean value of the BM blast rate is the high amount of BM blasts in patients in whom remission was not achieved.

No tumor lysis was detected in any patient. Other AEs of the patients are listed in Table 3.

Table 3. Adverse effects of the patients

Adverse Effect	First Line n (%)	RR n (%)	Maintenance n (%)
Neutropenia	13 (72.2)	10 (83.3)	4 (100.0)
Anemia	10 (55.5)	10 (83.3)	2 (50.0)
Thrombocytopenia	10 (55.5)	8 66.6)	1 (25.0)
Pneumonia	7 (38.9)	1(8.3)	-
FEN	6 (33.0)	4 33.3)	-
Vomiting	3 (16.6)	-	-
Fatigue	1 (5.5)	-	-
Nausea	1 (5.5)	1(8.3)	-
None	2 (11.1)	1(8.3)	1 (25.5)

FEN: Febrile neutropenia

Since Ven is metabolized by Cytochrome P450 3A4 (CYP3A4), dose reduction is needed when it is used with antifungals that cause CYP3A4 inhibition. The prophylactic antifungal use status of the patients who were evaluated in the present study and the distribution of their fungal infection history under AZA+Ven treatment is given in Table 4.

When evaluated with Fisher's Exact test, there was no statistically significant difference between prophylactic antifungal use and history of fungal infection under AZA+Ven (p=0.545)

The best response degree achieved by the patients under AZA+Ven treatment and the time to reach the best response are given in Table 5.

The OS data of the patients who were evaluated in the present study is given in Figure 1.

In the group receiving AZA+Ven in the first line, the average OS was 8.00 months (95% CI: 1.58-14.41), and was 7.00 months in the RR group (95% CI: 1.78-12, 21).

All patients in the maintenance group are alive and the median follow-up period was 12.50±6.02 months in this group (Mean±SD).

Table 4. Prophylactic antifungal use and history of fungal infection under AZA+Ven

First Line	n (%)
Prophylactic antifungal	
None	1 (5.6)
Fluconazole	13 (72.2)
Posaconazole	3 (16.7)
Caspufungin	1 (5.6)
History of fungal infection under AZA+Ven	
No	14 (77.8)
Yes	4 (22.2)
RR	
Prophylactic antifungal	
None	6 (50.0)
Fluconazole	5 (41.7)
Posaconazole	1 (8.3)
History of fungal infection under AZA+Ven	
No	8 (66.7)
Yes	4 (33.3)
Maintenance	
Prophylactic antifungal	
None	3 (75.0)
Fluconazole	0 (00.0)
Voriconazole	1 (25.0)
History of fungal infection under AZA+Ven	
No	4 (100.0)
Yes	0 (0.0)

Table 5. Best response and time to reach best response

Best Response	First Line n (%)	RR n (%)	Maintenance n (%)
CR	4 (22.2)	3 (25.0)	4 (100)
CRi	7 (38.8)	3 (25.0)	0
Refractory	3 (16.6)	2 (16.7)	0
NA	4 (22.2)	4 (33.3)	0
Time to best response (months) Mean±SD	3.18±1.32	3.00±1.41	
Median (min-max)	4.0 (1.0-5.0)	3.0 (2.0-4.0)	

CR:Complete Response. Cri:Complete Remission with Incomplete Blood Count Recovery, NA (Not Available): Patients who died before response assessment could be performed

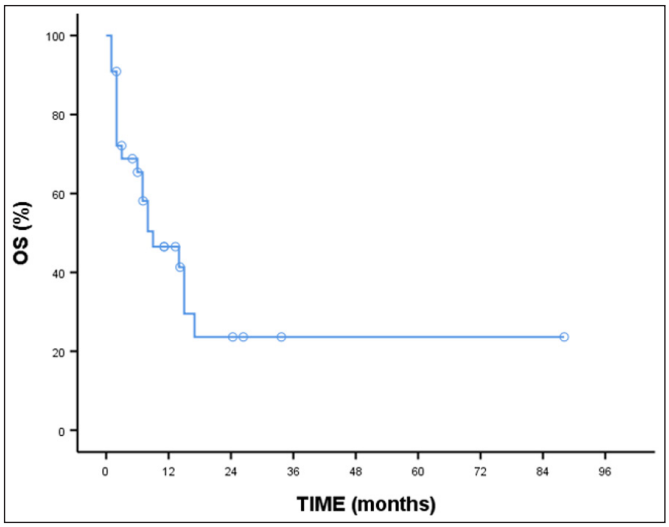

Figure 1. Overall survival data for patients. OS: Overall survival

Of the 34 patients evaluated in the study, 13 (38.2%) were alive and 21 (61.8%) were exitus. Among the causes of death of the patients in our study were COVID-19, FEN, progression, sepsis were defined and in 19% of patients, the cause of death could not be determined. The most common cause of death in both groups was COVID-19. The 2nd most common cause of death was FEN in the first line group, while it was progression in the RR group.

DISCUSSION

Various studies report that the HMA+Ven combination increases the response rates and OS in AML patients when compared to HMA monotherapy and is tolerated well.[9-12]

Combination therapies raise concerns regarding increased AE rates. Cytopenias are the most common AEs in hematological diseases. Although the risk of cytopenias is higher with the addition of Ven to HMA, it is generally managed easily.[9,13]

In the present study a significant deepening of cytopenias under AZA + Ven treatment was detected in patients with active leukemia, but the decrease in the maintenance group was not found to be statistically significant. The possible reason for this is that although leukemic cells are removed from the BM and peripheral blood through rapid apoptosis with the addition of Ven, BM recovery cannot occur at the same rate in patients with active leukemia. For this reason, cytopenias are detected more frequently in active leukemia patients, but the drug-induced suppression process is less common in the group receiving maintenance treatment and own intact BM.

In a Phase 3 study that compared patients receiving AZA+Ven Treatment with those receiving AZA monotherapy, it was reported that myelosuppression increased with the addition of Ven to AZA, but it did not deteriorate clinical outcomes.[14] In our study, despite cytopenias deepened at statistically significant levels in patients except the maintenance group and cytopenias levels reached Gr 3-4 in >50% of them, 23.5% of 34 patients died because of infectious reasons.

If the hematological recovery process under AZA + Ven treatment exceeds 2 weeks, a BM examination must be performed to evaluate whether the cytopenia is leukemia-related or drug-induced.[15] If blast increase is not detected, not every cytopenia might cause concerns. Especially in cases with a transformation from MDS to AML, cytopenias might continue after HMA + Ven treatment as evidence of reversion to the previous low-grade MDS.

The most common AE's observed in our study are shown in **Table 3**.When drug doses need to be reduced because of AEs, Jonas et al.[16] recommend shortening the duration of Ven or reducing the dose of HMA instead of reducing the dose of Ven, except in cases of drug-drug interaction.

Neutropenia due to the nature of the disease or drug effects is a common finding in AML. Even antibacterial, antifungal, and antiviral prophylaxis are used widely in AML, it is still not universally accepted.[17] But there are also publications arguing that mold-active antifungal agents should be mandatory for prophylaxis, especially in high-risk patients.[18] However, the intense drug-drug interaction between Ven and Azole-group antifungals, which are moderate-strong inhibitors of CYP3A4, caused that azoles were not allowed in many clinical studies in which HMA+Ven was evaluated.[9,19] In the study conducted by DiNardo et al.[9] in which Azoles were not allowed and routine antifungal prophylaxis was not used, prophylaxis was performed with alternative antifungals (e.g., Echinocandin) in 46% of the patients, and a low rate of clinically significant fungal infection was detected (8%). Considering the invasive fungal infection rates of around 4.1% under HMA monotherapy, these rates are acceptable.[20] For this reason, antifungal prophylaxis is generally recommended to be administered during severe neutropenia and for short periods, and prophylaxis with Echinocandins that have anti-aspergillus activity and do not require a reduction in the dose of Ven seem reasonable for these patients.[16,20,21] However, if Echinocandins are not preferred because of unavailability, high costs, and the necessity of intravenous administration, the use of Azole-group antifungals must not be avoided. Since Ven is metabolized by CYP3A4, dose reduction must be made when needed with antifungals that cause CYP3A4 inhibition. In light of some sub-studies in which drug interactions were evaluated, recommendations were made regarding the dose reduction that must be made in the Ven dose in case of azole use. Posaconazole is a strong CYP3A4 inhibitor and causes a 7.1-8.8-fold increase in the effectiveness of Ven when used together as a result of the increase in Cmax and decrease in its clearance.[22] If the use of antifungals that inhibit CYP3A4 strongly (e.g., voriconazole/posaconazole) is absolutely necessary, it is recommended to reduce the Ven dose by 75%, and if it is to be used with moderate CYP3A inhibitors (e.g., fluconazole and isavuconazonium sulfate) it is recommended to reduce the Ven dose by 50%. In patients whose treatment is interrupted because of toxicity that results from concurrent use with CYP3A4 inhibitors, Ven can be restarted 2-3 days after the discontinuation of the inhibitor.[23] In our study, no statistically significant difference was found between the history of fungal infection in patients who used prophylactic antifungals under AZA+Ven and those who did not. (**Table 4**)

It was reported in the study of Abishek et al.[10] that 43% of the patients were RR to the frontline HMA+Ven combination, refractoriness was detected in 5 patients in our study (14.7%), but it must be taken into consideration that 8 of 34 patients (23.5%) died before the first response evaluation.

When the response rates of the patients were evaluated in our study, CR+CRi was found to be 61% in the 1st line group and 50% in the RR group (**Table 5**). In the study of Abishek et al.[10] the CR+CRi rate was found to be 73% and was reported to be 60% in the study by DiNardo et al.[9] in high-risk subgroups such as secondary AML or with poor cytogenetics.

The time to reach the best response was determined as a median of 4 months (minimum 1 month - maximum 5 months) for the patients who could be evaluated for response and achieved CR/CRi in the 1st line group and a median of 3 months (minimum 2 months - maximum 4 months) in the RR group. In the study of Pollyea et al.[24] the median time to achieve the first response with the AZA + Ven Combination was reported as 1.2 months. The longer time to reach the best response in our study was found to have occurred because the routine of evaluating the response after the first cycle was not established in the early periods when the HMA+Ven combination was introduced into our center. The fact that the first response evaluations of the patients were made after the median 2.2 cycles (minimum 1-maximum 6 cycles) in our study might have caused the failure to identify patients who achieved responses in earlier cycles.

Concerns might be raised if morphological remission is not achieved after the first cycle because a very rapid response is expected from HMA+Ven treatment. However, if a significant decrease in the leukemic population is detected according to the baseline blast percentage after the 1st cycle and if Ven-based therapy is continued; BM examination is recommended again after the 2nd cycle. There are publications in the literature suggesting that if remission is still not achieved after the second cycle, success cannot be expected from the treatment and another treatment must be initiated.[10,11] However, there are also publications reporting that the time to reach the best response might be delayed under AZA+Ven treatment. In the study conducted by Winters et al., it was reported that the patients receiving AZA+Ven treatment in the off-trial group had the best response even after the 7th cycle. These results might be encouraging for patients who are frail and do not have many treatment options should not immediately despair at the lack of response in early cycles.

Routine BM control must be performed after the 4th cycle for patients with a response after the 1st or 2nd cycle of HMA+Ven treatment and every 6 months if there is no suspicion of relapse.[15,16]

In the management of myelosuppression in patients who achieved remission after the first cycle but neutropenia persists; recovery should be waited until the ANC reaches ≥500/µl, with a maximum of 14 days from day 29. In case of recurrent neutropenia, it was recommended to reduce the duration of Ven for subsequent cycles to 21 days and/or to reduce the dose of AZA, rather than to reduce the Ven dose.

A 20.5-month follow-up in the Viale-A study showed a significant increase in OS with combination therapy, with a median OS was 14.7 months in the AZA+Ven group and 9.6 months in the AZA+Placebo group (P <.001).[19] It was considered that the poor clinical history of the patients might be among the reasons why OS was found to be lower than the literature in our study. Five of 34 patients (14.7%) had a history of solid malignancy and 1 had a history of NHL. The fact that approximately 1/3 of patients have secondary AML is thought to lead to poor response to treatment and poor OS outcomes. In addition, the mean number of previous treatment lines received by the patients in the RR group was 3 (min 1-max 6) and 41.7% patients had a history of ASCT. A decrease in survival is an expected result as the risk factors of the patients increase. In the study of Abishek et al.[10] in which 29% of the patients were secondary AML and 81% of the patients were in the adverse risk group according to ELN Criteria, the median OS was 1.7 months in patients who were primary refractory to HMA+Ven and 2.3 months in relapsed patients.

Among the reasons why the response and survival rates demonstrated by real-life data were inferior to the results of clinical trials is the inclusion of patients with secondary AML, prior HMA history, advanced cardiovascular disease / heart failure, chronic obstructive pulmonary disease requiring regular oxygen use, advanced renal failure, active viral hepatitis, metabolic / immunological disease or other active malignancy in the off-trial group.

We think that another possible reason for the low OS found in our study is related to our tendency to use 200 mg dose of Ven in combination with antifungals in the early years when AZA+Ven combination was included in our clinical practice. The fact that only 9 (26.5%) of the 34 patients whose data were evaluated in our study were able to receive 400 mg Ven, might have led to low efficacy and results below the expected survival times. We think that if the number of patients is larger and if the Ven dose is not reduced unless absolutely necessary, it is possible to observe increased survival rates.

Limitations of the Study

The limitations of the present study were the small number of patients, the fact that the data were collected retrospectively, the lack of standardization in the use of antifungal prophylaxis, Ven doses and periods of follow-up BM biopsies because the patients were followed by different hematologists despite being in the same center.

CONCLUSION

HMA+Ven combination appears to be a candidate to become the standard treatment in the group of patients who are not suitable for intensive treatment, with its rapid-onset and sustainable efficacy and manageable AE spectrum.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was granted ethical approval by the University of Health Sciences Gülhane Scientific Researches Ethics Committee (Date: 27.06.2022, Decision No: 2022-249).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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