Efficacy of the Combination of Venetoclax and Azacitidine in Elderly of Frail Relapsed/ Refractory Patients with Acute Myeloid Leukemia, First Multi-Institutional Real World Experience from Turkey

Sude Hatun AKTIMUR[1], Ahmet Kursad GUNES[2], Osman AKIDAN[3], Ayse KARATAS[4], Mehmet TURGUT[5]

[1] Samsun Training and Researh Hospital, Department of Internal Medicine and Hematology, Samsun
[2] Ankara City Hospital, Department of Internal Medicine and Hematology, Ankara
[3] Karadeniz Technical University, Faculty of Medicine, Department of Internal Medicine and Hematology, Trabzon
[4] Hacettepe University, Faculty of Medicine, Department of Hematology, Ankara
[5] Ondokuz Mayıs University, Department of Hematology, Faculty of Medicine, Samsun, TURKEY

ABSTRACT

Acute myeloid leukemia (AML) usually seen in the elderly. The quest for effective, tolerable and durable response for the treatment of elderly or frail patients with AML resulted venetoclax combination. The aim of this study was to present here the experience and data for the use of venetoclax in combination with azacitidine in elderly or frail and unfit patients with relapse/refractory AML treated outside of a clinical trial. We retrospectively analyzed 30 consecutive elderly (≥ 65 years old) or frail patients with relapse/refractory AML, who failed at least one prior therapy for AML and treated with venetoclax in combination with 5-azacitidine at five institutions in Turkey between December 2018 - Januarry 2020. The patients were taken venetoclax at dose of 400 mg daily, and 75 mg/m^2/day azacitidine subcutaneously for 7 days per 28-day cycle. Complete remission (CR), incomplete blood count recovery (CRi), PR, overall survival (OS) and event free survival (EFS) were assessed. A total of 30 patients with a median age of 67 (range= 33-84) from 5 different centers were included in the final analysis. Overall response rate (ORR) was 63.3% (n= 19); 15 (50%) patients achieved CR or CRi and 4 (13.3%) patients achieved PR while 11 patients (37.7%) did not respond to therapy. Median 8 months follow-up, 6 months OS rate 66.7%, 1-year OS rate was 19.8% with a median OS was 7 months (95% CI: 7.8 -10.1). The mortality risk of patients under 60 is statistically significantly lower than those over 60 (p= 0.007, HR: 0.109 (95% CI: 0.022 - 0.55). Combination of venetoclax + HMA in patients with relapse refractory AML with poor performance score, it provided somewhat higher response rates and additionally, the responding patients benefited surival advantage when compared to non-responding patients.

Keywords: AML, Elderly, Venetoclax, Azacitidine, Survival

INTRODUCTION

Acute myeloid leukemia (AML) usually seen in the elderly. In this group of patients, the risk of having adverse genomic features and increased resistance of treatments are high.[1] Thus, ≥ 65 years old patients with AML generally respond poorly to conventional induction chemotherapy.[2] Additionally, the frailty of the older patients, such as comorbidities, compromised organ function and poor performance status could prevent them to take cytotoxic induction therapies.[3-5] As a result of the assessments of conventional therapies on elderly patients; currently we know "intensive chemotherapy does not benefit most older patients".[4] Therefore, standard of care for older or unfit patients is lower-intensity treatment regimens, including hypomethylating agents (HMAs) azacitidine or decitabine or low-dose cytarabine.

However, this treatment regimens needs longer time (3.5 to 4.3 months for best response) and yields lower response rate (10%-50%, including hematologic improvement), not curative and have short overal survival (OS) of less than 1 year.[6-9]

The quest for effective, tolerable and durable response for the treatment of elderly or frail patients with AML resulted venetoclax combination.[10] The rationale of this approach is based on the B-cell lymphoma 2 (BCL-2) protein, which plays pivotal role in the survival of AML blasts as a key regulator of the mitochondrial apoptotic pathway.[11-13] To maintain myeloblast survival, pro-apoptotic BAX must be sequestered with BCL-2, thus, BCL-2 inhibiton resulted with cell death via mitochondrial outer membrane permeabilization.[14] Efficiacy of venetoclax -a potent, selective, oral inhibitor of BCL-2- monotherapy in patients with relaps or refractory AML has been demonstared with tolerable safety profile.[15] Also, another critical anti-apoptotic protein for AML pathogenesis, MCL-1, which is a potential source of resistance to venetoclax treatment, is reduced with azacitidine.[16,17] Furthermore, synergistic effects of venetoclax and azacitidine combination has been assessed in pre-clinical models of AML cells[18], and the clinical efficiacy and tolerable safety profile has been shown with high complete remission (CR) + complete remission with incomplete blood count recovery (CRi) rate, low early mortality rates and overall survival (OS) extending beyond 17 months in elderly, frail and unfit AML patients who were not candidate for intensive chemotherapy.[10]

We present here the first "real world" experience and data from multiple center from Turkey for the use of venetoclax in combination with azacitidine in elderly or frail and unfit patients with relapse/refractory AML treated outside of a clinical trial.

PATIENTS and METHODS

We retrospectively analyzed 30 consecutive elderly (≥ 65 years old) or frail patients with relapse/refractory AML, who failed at least one prior therapy for AML and treated with venetoclax in combination with 5-azacitidine at five institutions in Turkey between December 2018-Januarry 2020. Study was approved by Institutional Review Board of Samsun Training and Education Hospital (IRB Approval Number: GOKA/2020/4/3).

Histologically confirmed AML patients with relapsed/refractory disease based on the assessment of bone marrow biopsy and circulating leukemia blasts were analyzed. Data were collected regarding patients clinical characteristics, prior and current therapies, cytogenetics, FLT-3 ITD mutation, adverse events and patients' outcomes. Genetic risk stratification was assessed according to European Leukemia Net combined cytogenetic and molecular profile.[19] The patients, who received leukopheresis and/or hydroxyurea before the treatment, for hyperviscosity symptoms with white blood cell (WBC) count is above 100.000/mm^3 in peripheral blood were not excluded. Patients response to therapy was defined according to International Working Group criteria.[20] According to control bone marrow biopsies (after first and third cycle), < 5% blast count was accepted as CR. CRi, PR and overall survival (OS) and event free survival (EFS) were assessed. The patients were taken venetoclax at dose of 400 mg daily, and 75 mg/m^2/day azacitidine subcutaneously for 7 days per 28-day cycle. The dose of venetoclax given to the patients was started as 100 mg and the target dose of 400 mg was reached by performing 3-day rump-ups. Patients who completed venetoclax + azacitidine treatment at least one cycle (4 weeks= 28 days) were included in the study.

Patients who received partial response in the complete response were included in the responded group, while patients who failed to respond were identified as resistant to treatment. The OS was calculated from the time of initial venetoclax dose to the time of death or last follow-up. EFS was defined from initial venetoclax to date of relapse, death or last follow-up.

Statistical Analysis

The data were analyzed with SPSS 21.0 (IBM, NY, USA). Chi-square test was used to compare categorical variables according to the groups. Chi-square test and Fisher Exact test were used to compare categorical variables according to mortality. Independent risk factors affecting mortality compared to OS time and risk factors affecting EFS

Table 1. Baseline patient and disease characteristics

	n= 30 patients
Age (Median)	67 (33-83)
Gender	
Male	18 (60%)
Female	12 (40%)
ECOG performance status	
1	3 (10%)
2	18 (70%)
3	9 (30%)
AML type	
De novo	27 (90%)
Secondary	3 (10%)
AML Cytogenetics	
Good	–
Intermediate	25 (83.3%)
Poor	5 (16.7%)
FLT-3 status	
Mutated	2 (6.7%)
Unmutated	24 (80%)
Unknown	4 (13.3%)
Bone Marrow Blast percentage	
< 30%	4 (13.3%)
30-50%	11 (36.7%)
> 50%	15 (50%)
Prior Antracycline Based Therapy	
Yes	18 (60%)
No	12 (40%)
Prior HMA	
Yes	14 (46.7%)
No	16 (53.3%)
Prior Allo HCT	
Yes	5 (16.7%)
No	25 (83.3%)
Prior Line of Therapy	
1	19 (63.3%)
2	6 (20%)
≥ 3	5 (16.7%)

time were examined by Cox Regression analysis. Log Rank (Mantel-Cox) test was used to determine whether there was a difference between survival times according to variables. Analysis results were presented as frequency (percent) for categorical data. All tests were 2-sided at a significance level of 0.05.

RESULTS

Baseline Patient and Disease Characteristics

A total of 30 patients with a median age of 67 (range= 33-84) from 5 different centers were included in the final analysis. Eighteen of the subjects were male (60%) and 12 were male. Majority of the patients (18 patients, 60%) had an Eastern Cooperative Oncology Group (ECOG) performance score of 2 and 9 patients, (30%) had ECOG performance score of 3. Twenty-seven patients (90%) had denovo AML while 3 patients (10%) had a secondary AML from antecent hematologic disorders. The majority of patients (25 patients, 83.3%) had intermediate risk disease, 5 of patients had adverse risk disease (17.7%) according to ELN risk stratification. No patients had a favorable risk disease. FLT3-ITD mutation was assessed in 26 (86.7%) patients, and positive results were seen in two patients (6.6%).

About 60% of the patients (18/30) were treated with prior antracycline based induction and 14 patients (46.7%) were treated with HMA's previously. Five of the patients (16.6%) had allogenic stem cell transplantation from HLA fully matched sibling donor after antracycline based induction as a consolidation treatment. 19 of 30 (63.3%) patients had prior 1 line of therapy while 6 of patients (20%) had 2 lines of therapy. Five patients (16.7%) presented with hyperviscosity symptoms, received hydroxyurea or leukopheresis, allopurinol was applied to prevent tumor lysis syndrome before treatment. Base bone marrow blast count was assessed in three groups; < 30%, 30% - 50%, and ≥ 50%, the results were 13.3% (n= 4), 36.7% (n= 11), and 50% (n: 15), respectively. None of the patients have had central nervous system involvement. Baseline patient and disease characteristics are summarized in Table 1.

Response to Venetoclax Combination Therapy

After a median follow up time of 8 months (1-12 months), the patients were received median 7 cycle of venetoclax and azacitidine combination therapy (range= 1-12). Overall response rate (ORR) was 63.3% (n= 19); 15 (50%) patients achieved CR or CRi and 4 (13.3%) patients achieved PR while 11

Table 2. Response to Venetoclax

	Total 30 patients
Number of Venetoclax cycle	
Median	7 (1-10)
Response to Venetoclax and Azacitidine therapy	
Resistant	11 (36.7%)
Partial Response	4 (13.3%)
Complete Response / CRi	15 (50%)
Number of Cycle (CR achieved)	
Median	3 (2-4)
1-year OS	
Rate	19.8%
Mean OS	8.2 months (95% CI: 7-9.4)
Median OS	7 months (95% CI: 7.8 -10.1)
1 year EFS	
Rate	14.4%
Mean EFS	6,2 months (95% CI: 4.8-7.7)
Median EFS	6 months (95% CI: 3.7-8.3)

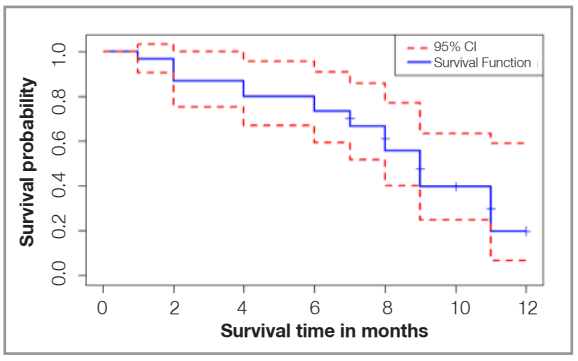

Figure 1. Overall survival (OS) data of all patients

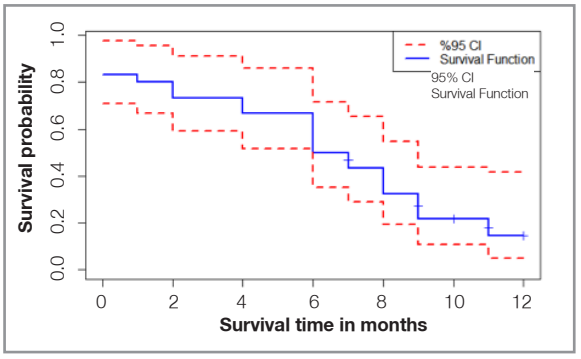

Figure 2. Event free survival (EFS) data for all patients

patients (37.7%) did not respond to therapy. Seven of the 15 patients (46.6%), who achieved CR, had responded to therapy after 3 cycle of the treatment.

Median 8 months follow-up, 6 months OS rate 66.7%, 1-year OS rate was 19.8% with a median OS was 7 months (95% CI: 7.8 -10.1). While 6-month EFS rate was 43.3%, 1-year EFS was 14.4%. Median EFS was 6 months (95% CI: 3.7-8.3). Response rates to venetoclax-azacitidine combination therapy are summarized in Table 2. The OS and EFS graphs of Venetoclax - azacitidine combination therapy are shown in Figure 1 and Figure 2.

The patients were divided into two groups as responders (n= 19, 63.3%) and non-responders (n= 11, 36.7%). There is a statistically significant difference between the median survival times according to the age of 60 and over 60 (11.4 months vs 5.1 months, p= 0.001).

The median survival time of one cycle of treatment was 9.9 months, while the median survival time of the two cycles was 4.6 months (p= 0.026). There is a statistically significant difference between the median survival times compared to the AML mutation (p= 0.003). The median survival time of those in the middle risk group was determined as 10.5 months, while the average survival time for those in the poor genetic risk group was 4.8 months.

Independent risk factors affecting 1-year survival were examined by Cox regression analysis. The mortality risk of patients under 60 is statistically significantly lower than those over 60 (p= 0.007, HR: 0.109 (95% CI: 0.022 - 0.55). The mortality risk of those receiving two cycles of treatments is statistically significantly higher than those receiving one cycles of treatment (p= 0.023, HR: 5.864 (95% CI: 1.272 - 27.024). Patients in the poor prognostic group compared to the AML mutation have a statistically significantly higher risk of mortality than those with moderate (p= 0.012, HR: 6.12 (95% CI: 1.501 - 24.956) (Table 3).

There is a statistically significant difference between 1-year survival according to the groups that respond to treatment and those who are non-responder (p= 0.004). The median survival time of those who responded to the treatment was 9.7

Table 3. Comparison of 12-month survival times by factors and cox regression results

	n	Responders	Non-responders	p	12-month survival (%95 CI)	Log-rank test p	HR (%95 CI)	p
Gender								
Female	12	8 (42.1)	4 (36.4)	1.000*	8.083 (6.024 - 10.142)	0.173	Reference	
Male	18	11 (57.9)	7 (63.6)		10.389 (8.708 - 12.07)		0.391 (0.093 - 1.639)	0.199
Age								
Under 60	10	4 (21.1)	6 (54.5)	0.108*	5.1 (3.055 - 7.145)	0.001	Reference	
Over 60	20	15 (78.9)	5 (45.5)		11.4 (10.611 - 12.189)		0.109 (0.022 - 0.55)	0.007
ECOG								
1	4	3 (15.8)	1 (9.1)	0.367**	---		---	
2	17	12 (63.2)	5 (45.5)		9.353 (7.35 - 11.356)	0.911	Reference	
3	9	4 (21.1)	5 (45.5)		8.667 (6.425 - 10.909)		1.082 (0.259 - 4.529)	0.914
AML Type								
Primary AML	27	18 (94.7)	9 (81.8)	0.537*	9.333 (8.106 - 10.561)	0.071	Reference	
Secondary AML	3	1 (5.3)	2 (18.2)		6 (1.111 - 10.889)		3.863 (0.765 - 19.512)	0.102
Allo HCT								
No	25	16 (84.2)	9 (81.8)	1.000*	8.92 (7.558 - 10.282)	0.751	Reference	
Yes	5	3 (15.8)	2 (18.2)		10 (6.494 - 13.506)		0.72 (0.089 - 5.851)	0.758
Cycle								
1	19	13 (68.4)	6 (54.5)	0.706**	9.947 (8.776 - 11.119)a	0.026	Reference	
2	6	3 (15.8)	3 (27.3)		4.667 (2.671 - 6.663)b		5.864 (1.272 - 27.024)	0.023
3 and more	5	3 (15.8)	2 (18.2)		10 (6.494 - 13.506)ab		1.371 (0.142 - 13.196)	0.785
AML Mutation								
Moderate	25	16 (84.2)	9 (81.8)	1.000*	10.52 (9.157 - 11.883)	0.003	Reference	
Poor	5	3 (15.8)	2 (18.2)		4.8 (3.012 - 6.588)		6.12 (1.501 - 24.956)	0.012
Antracycline Use								
No	12	7 (36.8)	5 (45.5)	0.712*	10.167 (9.112 - 11.221)	0.253	Reference	
Yes	18	12 (63.2)	6 (54.5)		8.833 (6.743 - 10.924)		2.422 (0.487 - 12.044)	0.280
HMA Use								
No	16	11 (57.9)	5 (45.5)	0.510**	8.375 (6.439 - 10.311)	0.469	Reference	
Yes	14	8 (42.1)	6 (54.5)		10.429 (8.787 - 12.07)		0.6 (0.143 - 2.514)	0.484
Flt3								
No	24	14 (73.7)	10 (90.9)	0.438**	9.333 (7.993 - 10.674)	0.405	Reference	
Yes	2	2 (10.5)	0 (0)		6.5 (3.035 - 9.965)		2.54 (0.295 - 21.866)	0.396
Not studied	4	3 (15.8)	1 (9.1)		8 (3.842 - 12.158)		2.517 (0.488 - 12.987)	0.270
Pretreatment leukopheresis hydroxiurea								
No	25	17 (89.5)	8 (72.7)	0.327*	10.28 (8.88 - 11.68)	0.056	Reference	
Yes	5	2 (10.5)	3 (27.3)		5.6 (3.084 - 8.116)		3.622 (0.851 - 15.422)	0.082

** Fisher Exact test, **Chi-square test*

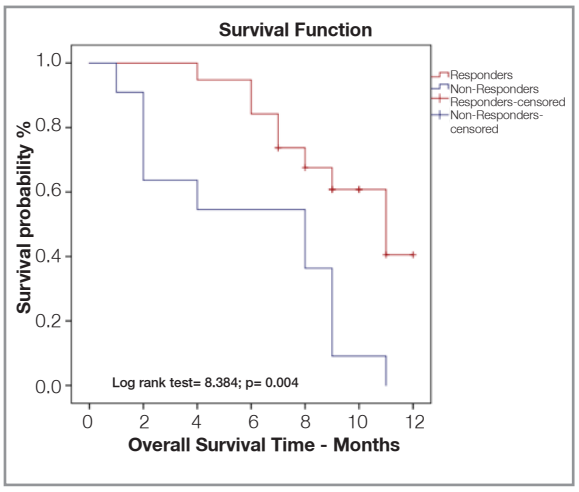

Figure 3. Comparison of patients who responded and non-responded in terms of OS

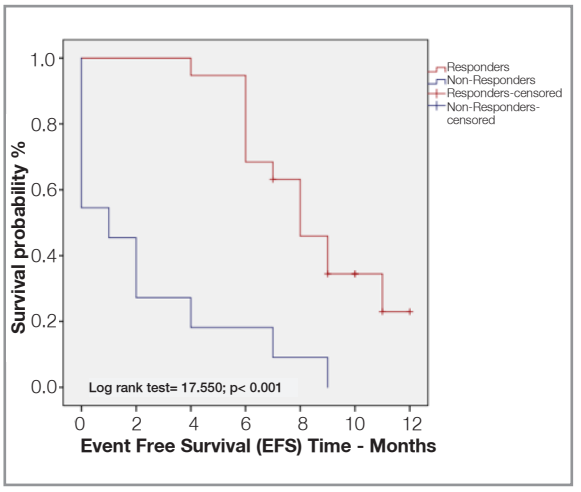

Figure 4. Comparison of patients who responded and non-responded in terms of EFS

months, while the median survival time of those who were non-responder was 5.9 months (Table 4 and Figure 3).

While the median duration of EFS existence of those responding to the treatment was 8.5 months, the median duration of EFS of the non-responder patients was 2.2 months (p< 0.001). As a result of the Cox regression analysis, the progression risk of those who responded to the treatment was statistically significantly lower than those who were non-responder (p< 0.001, HR: 0.204 95% CI: 0.086 - 0.482) (Figure 4).

Side Effects and Toxicities

Tumor lysis syndrome was not seen in any patient. All patients were hospitalized on the first cycle. During the 1st cycle, grade 3-4 neutropenia was observed in 25 patients (83.3%). Febrile neutropenia was detected in 21 patients (70%). One patient died at the end of the first cycle due to febrile neutropenia related sepsis and multi-organ failure. During the first cycle, grade 3-4 thrombocytopenia was detected in all patients. Median neutrophil (>1 x 10^9) and platelet (> 50 x 10^9) recovery time of the patients was determined as 23 days (17-39 days). The most common grade 1-2 side effects, other than hematological side effects, are; nausea-vomiting was found in 17 patients (56.7%) and diarrhea in 7 patients (23%).

DISCUSSION

In this multicenter retrospective study, we detected real-world data of Venetoclax + azacitidine combination other than clinical study in patients with advanced age, frail, relapse, refractory AML. Median after 8 months of follow-up, ORR was 63.3% (n= 19); 15 (50%) patients achieved CR or CRi and 4 (13.3%) patients achieved PR. The 6-month OS rate was 66.7%, the 1-year OS was 19.8%, and the median OS was 7 months. The 6-month EFS is 43.3%, the 1-year EFS is 14.3% and the median

Table 4. Comparison of 12-month survival times to groups

		Responders*	Non-responders*	p**	HR (%95 CI)***	p
OS	12 months	9.77 (8.561 - 10.979)	5.909 (3.722 - 8.096)	0.004	0.303 (0.122 - 0.757)	0.011
PFS	12 months	8.589 (7.427 - 9.75)	2.273 (0.421 - 4.124)	< 0.001	0.204 (0.086 - 0.482)	< 0.001

**Median (%95 CI). **Log-rank test. ***reference category (non-responders)*

EFS is 6 months. On overall survival, respondents to Venetoclax combination therapy, the AML cytogenetic risk group, age, and cycles of treatments were determined as independent risk factors.

Overall survival rates in AML decrease with age, independent of treatment.[21] With increased age, AML patients are more likely to experience unfavorable cytogenetics (Higher percentage of unfavorable cytogenetics), reduced CR recovery rates, and shorter remission duration and shorter median overall survival compared to younger patients.[22] In elderly AML, poor performance score, advance cytogenetics, secondary AML, FLT-3 mutation presence have been associated with poor prognosis.[23] Curative and therapeutic options are particularly limited in patients with advanced age, poor performance, relapsed AML patients.

Venetoclax is an oral BCL-2 inhibitor. In the treatment of AML, both in new diagnosed patients and in the relapse refractory group, it is promising with its impressive response rates and outcome data. In Phase 2 study evaluating venetoclax monotherapy in AML, CR / CRi was obtained in 19% of 32 patients who received 400-800-1200 mg venetoclax treatment, and bone marrow response was obtained in 19% of patients, although they did not meet the objective criteria. Due to low response rates and low duration of response times, there has been a trend towards combination therapies.[15] It has been shown that different protein expression panels can be used as a more objective biomarker in different risk classifications in order to evaluate AML risk categories objectively.[24] By determining protein expression profiles, the effects of venetoclax and its combinations can be more clearly understood.

In the Phase Ib / II study in the newly diagnosed AML, LDAC (20 mg/m^2 10 days) was combined with venetoclax 600 mg / day - in 28 days for AML patients with a median age of 74 years. Venetoclax was increased to 600 mg in 5 days with rump up in the first cycle. CR / CRi ratio was determined as 54% and median duration of response was 1.4 cycles, and better response rates were obtained in denovo AML than secondary AML. Median OS is 10.1 months. The 1-year OS was 27%.[25] In the multicenter phase 1b study, the combination of venetoclax and HMA (decitabine / azacitidine) was used in AML patients who are not suitable for elderly, new diagnosis, and intensive treatment.[10] In the median 15 months follow-up time, the CR / CRi rate was 68%, median response time was 1.2 cycle, Median OS was detected for 17.5 months. Recently, a placebo-controlled phase III study has been published evaluating the combination of Venetoclax and LDAC.[26] The new diagnosis was randomized to 211 patients, who were not eligible for intensive chemotherapy, in a 2: 1 ratio. ORR was 48% in the Venetoclax + LDAC arm, and 13% in the LDAC arm and OS advantage is shown. In summary, combination treatments of venetoclax with LDAC or HMA, the response rates obtained in newly diagnosed patients are historically better than LDAC and HMA alone.[9,27]

In November 2018, the FDA has confirmed venetoclax in combination with HMA or LDAC in AML patients over 75 years of age who are not eligible for intensive therapy.

In studies evaluating the effectiveness of Venetoclax in relapse refractory disease, CR / CRi ratio varies between 12 and 51%.[28,29] Aldoss et al published real-life data for the combination of venertoclax + HMA (decitabine / azacitidine) in 33 patients with relapse refractory AML.[29] The median age is 62, and the cytogenetic profile is included in the moderate / poor risk group in 87% of patients. In the group that received median 2 serial treatments, it was combined with 400 mg venetoclax and 75 mg/m^2 7 days azacitidine or 20 mg/25 days decitabine. Total response rate (ORR) is 64%, CR / CRi ratio is 51%. Patients had CR at the end of the 2nd cycle. There was no difference between the groups that responded and did not respond to the treatment in terms of anthracycline treatment, HMA treatment, and allogenic hematopoietic cell transplantation. This study is similar to our study in terms of design and patient profile and real-world data. In addition, the previously received treatments in the results of our study did not affect the venetoclax response. Although the ORR rates of our study are similar, the 1-year OS rates are quite high compared to our study. It is thought that this difference may be due to the poorer performance of the patients we included in our analysis.

In another analysis of real-world data published in March 2020 and performed in 40 relapsed refractory AML patients from 11 centers in Israel[30], Eighty-five percent of patients were combined with venetoclax HMA or LDAC. CR / CRi ratio is 52% in patients who received treatment for at least 2 months. The median OS was found to be 5.5 months after a median follow-up of 5.5 months. In this study, the number of recurrence cases after allogeneic transplant was found to be higher than our study (16.7% vs 42%). Patients' performance status is better than our group. Response rates and survival data in patients are similar to our study.

In a study evaluating the combination of venetoclax + azacitidine in 48 relapsed refractory AML patients, response to treatment, poor cytogenetic risk and age identified as an independent risk factor on survival.[31] In our study, it was shown that advanced age, cycle number and bad cytogenetic risk were independent factors on survival.

When the side effect profile is evaluated, the most common side effects are treatment-related hematological toxicity and prolonged cytopenias. Infective complications associated with febrile neutropenia have been observed. Similar to our study, venetoclax studies in newly diagnosed AML or relapse refractory disease were most frequently observed side effects are hematological toxicity and infection-related complications. The side effect and toxicity profile in our study are similar to those in the literature.

Our study has some limitations, it has a retrospective design, the number of patients is low, and there is no MRD analysis showing more detailed responses in patients. Except for routine AML cytogenetics and FLT-3, molecular-based IDH1 / 2, NPM1, RUNX1 and TP53 mutations could not be evaluated. However, performance scores are poor, advanced age and relapsed refractory patient group are strong aspects of the study.

Conclusion

In conclusion, the combination of venetoclax + HMA in patients with relapse refractory AML with poor performance score, along with the acceptable toxicity, it provided somewhat higher response rates and additionally, the responding patients benefited surival advantage when compared to non-responding patients. There is a need for randomized-prospective studies with a greater number of patients to evaluate the efficacy and outcome of the venetoclax HMA combination in relapsed refractory AML.

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Correspondence:

Dr. Sude Hatun AKTIMUR

Samsun Egitim ve Arastirma Hastanesi

Kisla Baris Bulvari

No: 199, 55090 Ilkadim

SAMSUN / TURKEY

e-mail: sudehatun@yahoo.com

Tel: (+90-532) 668 56 46

ORCIDs:

Sude Hatun Aktimur	0000-0002-7468-1721
Ahmet Kursad Gunes	0000-0001-5522-8342
Osman Akidan	0000-0002-4211-7309
Ayse Karadas	0000-0003-3955-2980
Mehmet Turgut	0000-0002-1036-0232