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Real world results of venetoclax combined with hypomethylating agents in relapsed/refractory AML

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Abstract. – OBJECTIVE: Relapsed/refractory AML cases are much more resistant to chemotherapy. Venetoclax is a highly sensitive BCL-2 inhibitor. It was aimed to evaluate the effects of venetoclax therapy on real-world R/R AML survival outcomes, the effects of the cytogenetic characteristics of the patients and previous clinical applications on treatment response, and venetoclax treatment toxicity.

PATIENTS AND METHODS: The study included patients who only received a venetoclax-based salvage on R/R AML patients from Turkey. The study included a total of 62 patients from 6 different centers in Turkey. Response to 2 cycles of venetoclax treatment was assessed by bone marrow blast rate. The demographic data, cytogenetic characteristics, AML type, MDS type, response rates and overall survival of the patients after venetoclax combination treatment were assessed. Median age of the patients was 65 (19-85). Mean number of prior treatments was 2.67 ±1.75.

RESULTS: 13 patients (21%) had a history of allogenic stem cell transplantation. 58 (93.5%) had received HMA therapy before venetoclax. 36 patients (58.1%) had de-novo AML, and 25 (40.3%) previously had MDS. Treatment response was evaluated as complete remission (n = 21, 33.9%), partial response (n = 17, 27.4%), and treatment failure (n = 24, 38.7%). Patients in the TF group were significantly more likely to have poor cytogenetic and to have received allogeneic transplants. The mean estimated overall survival after the venetoclax treatment was 9.13 ± 0.75 months.

CONCLUSIONS: The study population consisted of a group of patients who had relapsed or primary refractory disease with poor prognosis, despite numerous rounds of chemotherapy. It is our belief that the high response rates obtained with the combination of venetoclax/HMA, and having obtained positive results with poor risk patients, indicated a promising perspective for R/R AML patients.

Key Words:
Acute myeloid leukemia, Venetoclax, Relapsed, Refractory.

Abbreviations

AML: Acute Myeloid Leukemia; R/R: Relapsed and/or refractory; CR: Complete remission; PR: Partial remission; CRi: Complete remission with incomplete hematologic recovery; MLFS: Morphologic leukemia-free state; TF: Treatment Failure; OS: Overall Survival; Bcl-2: B-cell lymphoma 2; BCL-XL: B-cell lymphoma-extra-large; MCL-1: Myeloid leukemia cell differentiation protein-1; HMA: Hypomethylating agents; MDS: Myelodysplastic syndrome.

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of malignant diseases caused by uncontrolled clonal proliferation of myeloid precursor cells in the bone marrow. The overall survival (OS) rates in AML decrease markedly with age, where only 20% of patients over the age of 65 live longer than a year[1,2].

Blastic cells are much more resistant to chemotherapy in relapsed/refractory (R/R) AML patients due to various factors, including more commonly having poor cytogenetic features, a complex karyotype, a monosomal karyotype and high riskgene mutations, higher secondary AML and treatment-related AML incidence, and multiple drug resistance phenotypes[3,4].

The B cell lymphoma 2 (BCL-2) protein family prevents apoptotic cell death by reducing mitochondria outer membrane permeability. Overexpression of these proteins has been associated with tumor development, progression, and chemoresistance in AML[5].

Venetoclax is a BH3 mimetic that can be used orally and although it is a highly sensitive BCL-2 inhibitor, it lacks affinity for BCL-X_L and MCL-1. While MCL-1 is essential for cell survival in normal hematopoietic cells, BCL-2 is more prominent for the survival of blastic cells in AML. Targeting BCL-2 in AML enables a relative protection of normal hematopoietic cells[6,7].

The high tolerability of venetoclax has led to further studies investigating its use in combination with other agents[8,9]. Another study[10] showed that, when combined with hypomethylating agents (HMAs: azacitidine or decitabine), venetoclax significantly increased treatment response rates in first-line AML patients over 65 who were not eligible for intensive chemotherapy, especially in subgroups with poor prognosis, and reported that the overall median survival was 17.5 months.

This retrospective study primarily aimed to present real-world data from Turkey. Venetoclax is not licensed for the treatment of AML in Turkey, and it is administered on a named patient basis, often for the treatment of R/R AML. Considering that the response and side effects and management will be different for R/R patients when compared to first-line treatment, it was aimed to evaluate the effects of venetoclax therapy on the survival outcomes of real-world R/R AML patients, the effects of the cytogenetic characteristics of the patients and previous clinical applications on treatment response, and venetoclax treatment toxicity. It is believed that this study will make significant contributions to the literature by presenting the most extensive multicenter real-world venetoclax experience on R/R AML patients from Turkey.

Patients and Methods

Study Design and Setting of the Study

We retrospectively evaluated patients aged ≥18 years who received treatment for R/R AML in hematology clinics over a 12-month period between February 2019 and January2020. The study included patients who only received venetoclax-based salvage therapy in combination with hypomethylating agents (HMAs). The study included a total of 62 patients from 6 different centers in Turkey. The demographic data, bone marrow blast percentage at the time of AML diagnosis, cytogenetic findings, AML type (primary/secondary), previous presence of myelodysplastic syndrome (MDS), and (for those who previously had MDS) MDS type and blast percentages of the patients were recorded.

Treatments applied prior to and in combination with venetoclax therapy, toxicities and complications that developed during venetoclax therapy, and pre- and post-venetoclax therapy bone marrow blast percentages were retrospectively evaluated. Last follow-up date was August 2020 for survived patients. Survival times were calculated according to this date.

The treatment regimens received prior to the venetoclax therapy were as follows: "3+7": Cytarabine and anthracycline combination, HMA: Hypomethylating agents (decitabine or azacitidine), FLAG: Fludarabine + cytarabine + G-CSF ± idarubicin, EMA: Etoposide + cytarabine + mitoxantrone, single agent Clofarabine and allogenic stem cell transplantation.

AML and MDS diagnoses were made according to the 2016 World Health Organization classifications1[11]. The genetic risk categories were defined according to the European Leukemia Net risk stratification[12].

Response evaluation after 2 cycles of venetoclax treatment was assessed by bone marrow blast percentage, peripheral blood smear, and complete blood counts in all the patients. Treatment response was defined according to the International Working Group (IWG) criteria, as follows[13]: complete remission (CR), where the

bone marrow blast percentage was below 5% (in this study, incomplete CR responses where considered as CR); partial response (PR), where the bone marrow blast percentage was above 5%, but the blast percentage decreased by more than 50% when compared to before treatment; and treatment failure (TF), where the bone marrow blast percentage increase when compared to before treatment. In the current study, CR and PR were classified as positive treatment response.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was granted ethical approval by the Scientific Ethics Committee of Mersin University Faculty of Medicine (date of ethics committee: 20.02.22020, decision number: 78017789/050.01.04/E.1321381).

Statistical Analysis (for the 3 Groups)

SPSS 23.0 (IBM, Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, standard deviation, and minimum-maximum. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Tests). Independent Student's *t*-test was used for binary variables and One-way Anova test was used for groups with normal distribution, while Chi-square test and Fischer's Precision Test were used for comparison of categorical variables. While Mann-Whitney U test was used for binary variables in groups that did not fit normal distribution, Kruskall Wallis tests were used for more than two variables. Bonferroni analysis was used in Post-Hoc analyzes to determine the source of the difference between groups. Kaplan-Meier analysis and Log Rank tests were used for survival analysis. Statistical significance was accepted as $p < 0.05$.

Results

Patient Characteristics

A total of 62 patients who were followed up with the diagnosis of relapsed or refractory AML from 6 different centers in Turkey and given rescue treatment containing venetoclax between 10 October 2019 and 10 February 2020 were evaluated retrospectively. The median age of the patients was 65 years (range 19-85), and 28 patients (45.2%) were female. Among the entire patient cohort, there were 36 (58.1%) *de-novo* AML patients and 25 (40.3%) patients with previous MDS. One patient who developed secondary AML had lung cancer and another had colon cancer. Moreover, 28 patients (45.2%) died during the follow-up (Table I). The salvage therapy history and disease characteristics of the patients are given in Table I.

Table I also presents the cytogenetic characteristics of the patients at the time of AML diagnosis; number and order of chemotherapy; TLS development during venetoclax treatment; presence and frequency of neutropenic fever; increase in anemia, neutropenia, and thrombocytopenia; and survival analysis.

Treatment Response Assessment

Treatment response was evaluated (according to the IWG criteria) after 2 cycles of venetoclax + HMA therapy, as CR (n = 21, 33.9%), PR (n = 17, 27.4%), and TF (n = 24, 38.7%). The comparison of the baseline characteristics of the subjects according to the IWG classifications (CR, PR, and TF) revealed the following.

The 3 groups were not significantly different in terms of the AML type, presence of MDS (or MDS type), pre-venetoclax salvage treatments (3+7, FLAG, HMA, EMA), or venetoclax-related toxicity (tumor lysis, increased anemia, increased thrombocytopenia, increased neutropenia) ($p > 0.05$) (Table II).

Patients in the TF group were significantly more likely to have poor cytogenetic ($p < 0.05$) and to have received allogeneic transplants ($p = 0.018$) and EMA treatment ($p = 0.000$) prior to the venetoclax treatment when compared to those in the CR and PR groups. Moreover, survival was significantly lower in the TF group when compared to the positive treatment response groups ($p < 0.05$), whereas the incidence of neutropenic fever ($p = 0.006$) and pneumonia ($p = 0.012$) was significantly higher (Table II).

The 3 groups were not significantly different in terms of number of treatments before venetoclax, number of chemotherapy cycles before venetoclax, and duration (months) between AML diagnosis and initiation of the venetoclax treatment ($p > 0.05$) (Table II).

Table I. Patient characteristics.

Patient characteristics		N = 62 (100%)
Age, median (min-max)		65 (19-85)
Gender	Female	28 (45.2)
	Male	34 (54.8)
Genetic risk category	Favorable	13 (21)
	Intermediate	36 (58.1)
	Poor	13 (21)
AML type	De novo	36 (58.1)
	Secondary	26 (41.9)
Presence of prior MDS	Present	25 (40.3)
MDS type	MDS-MLD	4 (16)
	MDS-EB-1	6 (24)
	MDS-EB-2	8 (32)
	MDS/MPN	7 (28)
Outcome	Survived	34 (54.8)
	Died	28 (45.2)
Number of treatments prior to venetoclax, median (min-max)	2 (1-9)	
Total number of treatment cycles prior to venetoclax, median (min-max)	7 (2-36)	
Treatments before venetoclax	7 + 3	41 (66.1)
	ASCT	13 (21)
	HMA	58 (93.5)
	FLAG	28 (45.2)
	Clofarabine	14 (22.6)
	EMA	11 (17.7)
Treatment in combination with venetoclax	Azacitidine	34 (54.8)
	Decitabine	28 (45.2)
Toxicity with venetoclax	Tumor lysis	6 (9.7)
Neutropenic fever	53 (85.5)	
Pneumonia	44 (71)	
Increased anemia	35 (56.5)	
Increased thrombocytopenia	37 (59.7)	
Increased neutropenia	45 (72.6)	
Post-venetoclax response evaluation	CR	21 (33.9)
PR	17 (27.4)	
TF	24 (38.7)	
Time between initiation of the venetoclax therapy and death (months)	5.05 (0.62-14.41)	

However, the groups were significantly different in terms of the number of rounds of venetoclax treatment, pre-venetoclax bone marrow blast percentage, neutropenic fever, pre-venetoclax PLT, and survival time (months) after venetoclax treatment ($p < 0.05$). Furthermore, the pre-venetoclax bone marrow blast rate was significantly lower in the CR group when compared to the PR ($p = 0.034$) and TF ($p = 0.000$) groups ($p < 0.05$). Neutropenic fever was significantly more prevalent in the TF patients than in the CR patients ($p < 0.05$). The mean pre-venetoclax PLT result of the PR group was significantly higher than that of the TF group ($p < 0.05$). Moreover, the time between the initiation of venetoclax treatment and death was significantly lower in the TF group when compared to the CR ($p = 0.000$) and PR ($p = 0.002$) groups ($p < 0.05$) (Table II).

Survival Analysis

The estimated median OS of the patients in the study was 37.11 ± 7.78 months. The 1-year survival rate was 82.3% and the 3-year survival rate was 56.5%. The median estimated OS after initiation of the venetoclax treatment was 9.13 ± 0.75 months, while the estimated 1-year survival rate after the venetoclax treatment was 54.8%. The analyses demonstrated that the patients in the TF group had significantly poorer OS outcomes, as measured both from the time of AML diagnosis ($p = 0.002$) and initiation of the venetoclax treatment ($p = 0.000$), when compared to patients in the PR and CR groups ($p < 0.05$) (Table III). Survival analyses are presented in Figure 1 and Table IV.

As determined after the venetoclax treatment, the 1-year estimated survival rates were as follows: 90.5% for the CR group, 76.5% for the PR group and 8.3% for the TF group (Figure 2, Table V).

Table II. Assessment of the treatment response (Univariate analyses)*.

Patient characteristics	CR (n = 21) n (%)	PR (n = 17) n (%)	TF (n = 24) n (%)	Total (n = 62) n (%)	*p*-value
Gender					0.306
Female	11 (52.4)	5 (29.4)	12 (50.0)	28 (45.2)	
Male	10 (47.6)	12 (70.6)	12 (50.0)	34 (54.8)	
Genetic risk					0.017
Favorable	5 (23.8)	6 (35.3)	2 (8.3)	13 (21.0)	
Intermediate	14 (66.7)	9 (52.9)	11 (45.8)	34 (54.8)	
Poor	2 (9.5)	2 (11.8)	11 (45.8)	15 (24.2)	
AML type					0.994
De novo	12 (57.1)	10 (58.8)	14 (58.3)	36 (58.1)	
Secondary	9 (42.9)	7 (41.2)	10 (41.7)	26 (41.9)	
Presence of prior MDS	8 (38.1)	7 (41.2)	10 (41.7)	25 (40.3)	0.967
MDS type					0.220
MDS-MLD	0 (0.0)	3 (42.9)	1 (11.2)	4 (16.0)	
MDS-EB-1	3 (33.3)	0 (0.0)	3 (33.3)	6 (24.0)	
MDS-EB-2	3 (33.3)	3 (42.9)	2 (22.2)	8 (32.0)	
MDS/MPN	3 (33.3)	1 (14.2)	3 (33.3)	7 (28.0)	
Treatments before venetoclax					
HMA	18 (85.7)	16 (94.1)	24 (100.0)	58 (93.5)	0.150
3 + 7	12 (57.1)	12 (70.6)	17 (70.8)	41 (66.1)	0.564
ASCT	5 (23.8)	0 (0.0)	9 (37.5)	14 (22.6)	0.018
FLAG	8 (38.1)	6 (35.3)	14 (58.3)	28 (45.2)	0.250
MAC	0 (0.0)	1 (5.9)	10 (41.7)	11 (17.7)	0.000
Treatment in combination with venetoclax					0.029
Azacitidine	7 (33.3)	11 (64.7)	17 (70.8)	35 (56.5)	
Decitabine	14 (66.7)	6 (35.3)	7 (29.2)	27 (43.5)	
Outcome					0.000
Survived	19 (90.5)	13 (76.5)	2 (8.3)	34 (54.8)	
Died	2 (9.5)	4 (23.5)	22 (91.7)	28 (45.2)	

*$p < 0.05$, chi square.

Discussion

The most important issue for R/R AML patients is that no proven optimal treatment option exists yet. Currently, the most important cause of AML treatment failure is recurrence. For younger patients, the goal of treatment is to provide a bridge therapy for allogeneic transplantation, while for non-transplant candidates, treatment options aim to improve the quality of life, cause less toxicity, and extend survival. In patients over 60 years of age, the CR rate was around 28%, even with intensive chemotherapy; however, new studies suggested that CR rate can be up to 37% with liposomal daunorubicin-cytarabine[14].

Table III. Survival from the time of AML diagnosis and estimated survival after the initiation of venetoclax treatment (n = 62)*.

	Median				1-year survival (%)	3-year survival (%)
			95% Confidence interval			
	Estimated Median	SD	Lower limit	Upper limit		
Duration from AML diagnosis until venetoclax treatment (months)	37.11	7.78	21.84	52.38	82.3	56.5
Survival after venetoclax treatment (months)	9.13	0.75	7.65	10.62	54.8	–

*Log-rank test.

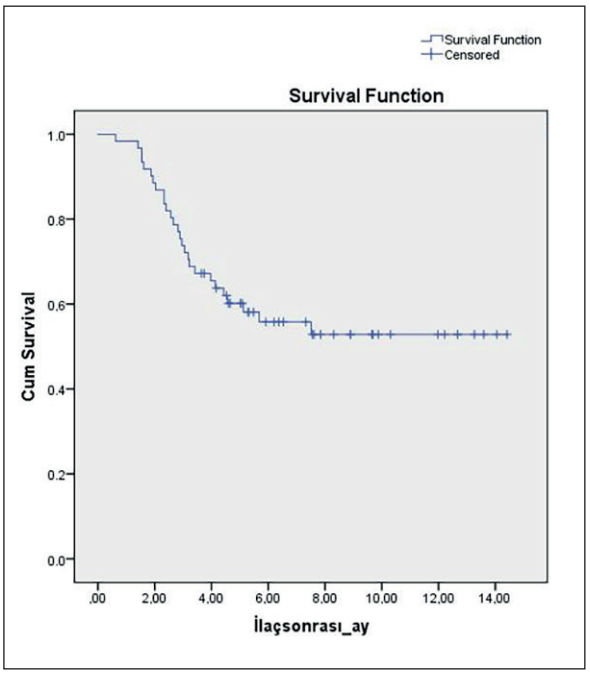

Figure 1. Estimated survival after venetoclax treatment.

A study by Di Nardo et al[15] of 145 AML patients reported that the first-line venetoclax + HMA treatment resulted in a CR+CRi rate of 68%. Another first-line treatment study investigating the outcomes of venetoclax-LDAC treatment reported the CR+CRi rate as 54% overall and 60% for patients older than 75 years[16]. A study by Mei et al[17] which included only R/R AML patients revealed that, for venetoclax + HMA treatment, the total response rate (CR+CRi+MLFS) was 64%. Thus, venetoclax treatment was able to achieve an increased treatment response without increased early mortality. Early phase results of venetoclax in combination with both azacitidine and LDAC were recently validated by randomized controlled phase 3 studies[16,18].

In the current study, after 2 rounds of venetoclax-HMA treatment, 21 (33.9%) of the 62 patients achieved CR, while 17 (27.4%) achieved PR, and 24 (38.7%) had TF, with an average treatment response rate of 61.3% (CR + PR). The study group consisted of patients who had exhausted all their treatment options, relapsed after intensive treatments and salvage therapy, and had received a median of 2 types of treatment prior to the venetoclax. The literature indicated that the expected survival of such patients was less than 10%, and the current results demonstrated that venetoclax-HMA therapy can serve as a bridge therapy option for transplant candidates and is associated with longer-term survival for older patients[19].

It has been well-established that secondary AML has poor prognosis[20]. In the current study, secondary or de-novo AML did not negatively affect venetoclax response. In the patient cohort, most patients with secondary AML were MDS-transformed. The MDS-transformed AML patients had high R-IPSS scores and a high mean bone marrow blast percentage (8%), with the majority having previously received HMA ther-

Table IV. Assessment of differences between survival from the time of AML diagnosis and survival after the initiation of venetoclax treatment*.

	Median				1-year survival (%)	3-year survival (%)	*p*-value
		95% confidence interval					
	Estimated median	SD	Lower limit	Upper limit			
Experimental group (survival until the time of AML diagnosis)							
CR	28.95	7.91	13.45	44.46	100.0	90.4	0.002
PR	16.72	1.91	12.97	20.48	88.2	76.4	
TF	5.36	2.35	30.75	39.97	62.5	4.2	
Experimental group (survival after the initiation of venetoclax treatment)							
CR	12.98	0.71	11.57	14.38	90.5	–	0.000
PR	11.57	1.22	9.16	13.97	76.5	–	
TF	3.17	0.42	2.34	4.00	8.3	–	

*Log-rank test.

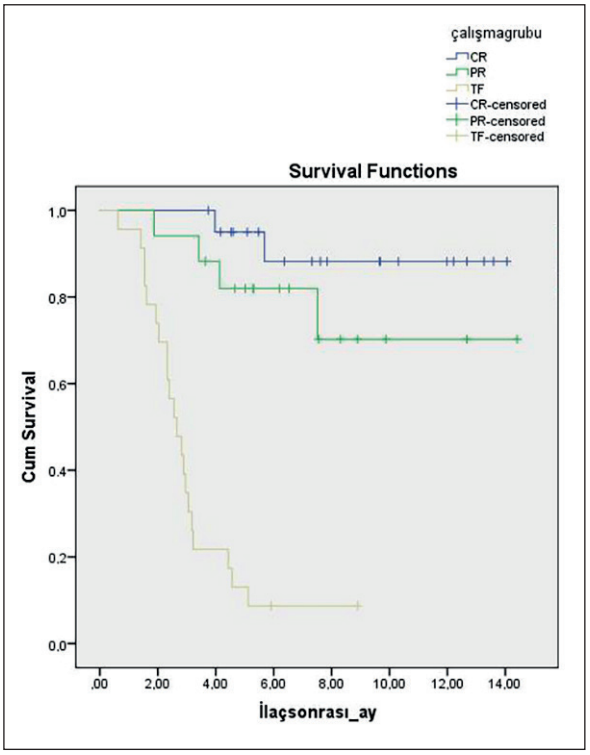

Figure 2. Effect of treatment response after venetoclax treatment on estimated survival.

apy. However, there was no finding that having previous MDS, different MDS subtypes, or a bone marrow blast percentage during MDS affected the venetoclax treatment response. These data were consistent with the literature[17,20]. It is our belief that these successful results in patients with MDS-transformed or secondary AML may have been associated with the synergistic effect of venetoclax + HMA on poor cytogenetic risk. The fact that age was not significantly associated with the treatment outcome was ascribed to the fact that the younger patients were those who had exhausted all other treatment options.

Patients with poor genetic risk were more likely to be in the TF group and treatment response was low in patients who relapsed after allogeneic transplantation. These data were consistent with the literature[16,20]. In the current study, among the 15 patients with poor cytogenetic risk, 2 achieved CR and 2 achieved PR. Furthermore, among the 34 patients in the intermediate risk category, 14 achieved CR and 9 achieved PR. These results demonstrated that venetoclax + HMA was effective in the different patient subgroups, including patients with high cytogenetic risk. These real-world venetoclax treatment results in patients with multiple relapses and negative cytogenetic characteristics showed very promising results.

The treatment-resistant TF group consisted of patients who had relapsed after allogeneic transplant and received intensive chemotherapy, such as EMA chemotherapy (usually after both 3+7 and FLAG). Therefore, neutropenic fever and pneumonia (the most important causes of mortality in this group) were statistically higher in this group due to long-term non-remission and

Table V. Assessment of the differences between the experimental groups and numerical parameters*.

	CR (1) (n = 21) mean ± SD (min-max)	PR (2) (n = 17) mean ± SD (min-max)	TF (3) (n = 24) mean ± SD (min-max)	Total (n = 62) mean ± SD (min-max)	*p*-value	Post-hoc significance
ECOG (F)	1.71 ± 0.90 (0-3)	2.0 ± 0.89 (1-3)	1.95 ± 0.80 (1-3)	1.90 ± 0.86 (0-3)	0.444	NS
Age (x^2)	61.38 ± 16.31 (24-79)	64.0 ± 12.88 (34-85)	57.75 ± 17.43 (19-79)	60.69 ± 15.87 (19-85)	0.575	NS
Number of treatments before venetoclax (x^2)	2.23 ± 1.51 (1-6)	2.52 ± 1.94 (1-9)	3.16 ± 1.76 (1-5)	2.67 ± 1.75 (1-9)	0.130	NS
Total number of treatment cycles applied prior to venetoclax (x^2)	6.47 ± 4.17 (2-16)	7.05 ± 4.23 (2-16)	10.08 ± 7.07 (3-36)	8.03 ± 5.65 (2-36)	0.069	NS
Duration from AML diagnosis until venetoclax treatment (months)	16.87 ± 7.85 6.20 (0.07-104.9)	7.88 ± 5.62 7.38 (0.07-22.0)	12.74 ± 10.40 11.88 (0.1-37.4)	12.81 ± 17.77 17.77 (0.07-104.9)	0.305	NS
Time between initiation of the venetoclax therapy and death (months)	8.27 ± 3.58 7.61 (3.74-14.05)	6.78 ± 3.30 6.20 (1.87-4.41)	3.32 ± 2.23 2.74 (0.62-9.88)	5.95 ± 3.70 5.05 (0.62-14.41)	0.000	1-3, $p = 0.000$ 2-3, $p = 0.002$

*$p < 0.05$, F: 1-way ANOVA, x^2: Kruskal-Wallis test, NS: Not significant..

neutropenia. Tumor lysis syndrome, which is associated with venetoclax therapy in patients with chronic lymphocytic leukemia, was found to be uncommon in the current patient cohort, which was consistent with the literature[17,19].

The already mentioned study by Di Nardo et al[15] of 145 AML patients found the OS to be 17.5 months for all their first-line patients[19]. Another first-line treatment study demonstrated that patients treated with venetoclax + LDAC had a median survival of 10.1 months[16]. In the current study, the 1-year survival rate after venetoclax treatment was determined as 54.8%. The survival outcomes herein were consistent with those in the literature and suggested very promising results for the R/R patients who had exhausted all other treatment options. Furthermore, the current study demonstrated the positive effects of the response rate on survival, and that the prognoses of the CR patients were better than those of the PR patients. This suggested that the survival outcomes would improve with early-stage applications that would be aimed at achieving a higher CR rate. Moreover, it was observed that PR, which was considered as a suboptimal treatment response in first-line treatment, had a positive effect on survival by providing disease control in R/R AML.

Conclusions

The current study population consisted of a group of patients who had relapsed or had primary refractory disease with poor prognosis, despite numerous rounds of chemotherapy. It was our belief that the high response rates obtained with the venetoclax/HMA combination, and the obtained positive results with poor risk patients, indicated a promising perspective for R/R AML patients. There is still a significant gap in the treatment of AML, and it is our belief that early clinical access to innovative treatments, such as venetoclax, will significantly contribute to the life course of patients. We think that our study will make significant contributions to the literature by presenting the most extensive multicenter real-world venetoclax experience on R/R AML patients from Turkey.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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