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ORIGINAL ARTICLE

Combination of Venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia: A case series from a single center

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Summary

Purpose: *Venetoclax (VEN) is an oral selective inhibitor of antiapoptotic protein B-cell leukemia/lymphoma-2 (BCL-2).*

Methods: *We report 7 relapsed/refractory (R/R) acute myeloid leukemia (AML) patients treated with venetoclax and hypomethylating agents (HMA).*

Results: *More than half of the patients could go on with venetoclax for only a few months.*

Conclusion: *Using venetoclax combined with HMA in R/R AML should be kept in mind as an alternative salvage option.*

Key words: *venetoclax, relapsed/refractory, acute myeloid leukemia, salvage chemotherapy*

Introduction

Venetoclax is an oral selective inhibitor of antiapoptotic protein B-cell leukemia/lymphoma-2 (BCL-2). It is overexpressed in acute myeloid leukemia (AML) and associated with poor prognosis [1]. Venetoclax has been shown to be effective in combination with a hypomethylating agent or low dose cytarabine for newly diagnosed elderly AML patients who were ineligible for intensive chemotherapy [2]. Clinical trials on using venetoclax in combination with cytarabine or hypomethylating agents for relapsed/refractory (R/R) AML are encouraging [3,4]. Furthermore, AML is a common form of acute leukemia in adults. The clinical outcome of adult AML patients remains poor [5]. Prognosis in R/R AML patients is worse, with no standard salvage chemotherapy protocol. Clinical trials may also be chosen as the first treatment approach in R/R AML patient for both the fits and unfits [6].

Venetoclax is a highly selective inhibitor of antiapoptotic protein BCL-2 which plays a significant role in the apoptotic pathway [7,8]. The BCL-2 family, contained in both pro-apoptotic and anti-apoptotic members, acts as regulator of apoptosis [9]. BCL-2 protein which maintains myeloblast survival is high in leukemia stem cell population [10] and has been related to poor prognosis in AML patients [11,12]. Venetoclax is approved by the United States Food and Drug Administration (FDA) in the combination treatment with a HMA (azacytidine or decitabine) or low dose cytarabine for newly diagnosed AML patients who are 75 years or older, or unfit for standard intensive induction therapy [13].

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Concomitant inhibition of DNA methyltransferase and BCL-2 induce apoptosis in AML cells [14]. BCL-2 inhibitors have potential effect to sensitize AML cells to HMA [15,16].

In this study, we retrospectively analyzed 7 adult R/R AML patients who failed at least one prior therapy for AML treated with venetoclax in combination with decitabine or 5-azacytidine at the Hematology Clinic and Bone Marrow Transplantation Unit, University of Health Sciences, Ankara Dr. Abdurrahman Yurtaslan Oncology Education and Research Hospital between 2018 and 2020.

Case I (Table 1)

A 45-year-old male patient was diagnosed with myelodysplastıc syndrome (MDS) with excess blasts-2 (MDS-EB-2) in November 2019. Karyotyping showed 46, XY, del 5q31: 50%, 7q22.1-q22.2 and 7q31.2: 62 %. After 3+7 induction chemotherapy with cytarabine and idarubicin, he had recurrent pneumonia, preseptal cellulitis, a breast abscess and catheter infection. Although he was not in remission, he was unfit for an intensive re-induction chemotherapy. His treatment was started on therapeutic 5-azacytidine. After receiving two cycles of azacytidine, he had stil refractory disease. He was shifted to decitabine in April 2020 and received one cycle of decitabine. Venetoclax was also started in April 2020. The patient was cytopenic due to disease at the beginning of the combined therapy. He took nearly 1 month of venetoclax and then required intensive care unit hospitalization for gastrointestinal bleeding and died on April 30, 2020.

Case II (Table 1)

A 40 -year-old female was treated with radiotherapy and chemotherapy for Ewing sarcoma in 2013. She was diagnosed with secondary AML in March 2019 (normal karyotype). After receiving 3+7 induction chemotherapy (cytarabine, idarubicin), she achieved complete molecular remission and she then had FLAG chemotherapy (fludarabin, Ara-C, G-CSF) as consolidation and underwent allogeneic stem cell transplantation with a full-matched donor in July 2019. She had molecular relapse in November 2019. She received two cycles of 5-azacytidine and 2 doses of donor lymphocyte infusion (DLI). She took nearly 4 weeks of venetoclax. Due to persistent grade 3 cytopenia and infection (pneumonia, cytomegalovirus reactivation) venetoclax was discontinued. She received CD34-selected stem cell boost. Because of the refractory disease, she received Cloamsa (Clofarabine, Ara-C, Amsacrine) as a salvage chemotherapy, developed sepsis and passed away in June 2020.

Case III (Table 1)

A 45-year-old male was diagnosed with AML in September 2019 (46, XY,del 5q31: 50%). After 3+7 induction chemotherapy wıth cytarabıne and idarubicin, he developed septic shock/multiorgan failure. He received 5-azacytidine maintenance for two cycles and achieved complete remission. He developed relapsed disease in December 2019. The treatment was shifted to decitabine and venetoclax in January 2020. He completed two cycles of decitabine. The patient achieved complete remission and he received two-month therapy with venetoclax. He required hospitalization for pneumonia and developed sepsis with multiorgan failure and passed away in March 2020.

Case IV (Table 1)

A 30-year-old female was diagnosed with AML in April 2019 (normal karyotype). After receiving 3+7 induction therapy with cytarabine and idarubicin and FLAG chemotherapy, she achieved complete molecular remission. She underwent full-matched-allo-stem cell transplantation (SCT) in August 2019. Her disease relapsed in March 2020 and she was started on venetoclax in combination with 5-azacytidine. She received 3 cycles of 5-azacytidine and two doses of DLI. She took venetoclax for around 3 months (5 days ramp up: 100-200-400 mg). The patient was thrombocytopenic due to disease at the initiation of venetoclax. Venetoclax was well tolerated at a dose of 200 mg daily except for cytopenia (mainly grade 3 thrombocytopenia and neutropenia), infection (recurrent tooth abscess) requiring hospitalization. Her last evaluation revealed grade 3 thrombocytopenia with 43% donor chimerism. Bone marrow biopsy was planned to evaluate the disease activity at the end of the 4th course of 5-azacytidine.

Case V (Table 1)

A 20-year-old male was diagnosed with AML in December 2018. He was refractory to 3+7 therapy with cytarabine and idarubicin, and FLAG chemotherapy. The patient underwent matched-related-allogeneic stem-cell transplantation in February 2019 (normal karyotype). His disease relapsed in September 2019. He was started on combination treatment of 5-azacytidine and Ara-C (200mg/day) for 3 days because of leukocytosis >100000 mm^3) with venetoclax (amp up: 100; 200; 400 mg). Following Cloamsa chemotherapy protocol (Clofarabine, Ara-C, Amsacrine), he had a second matched-related-allogeneic stem-cell transplantation in December 2019. He developed cytomegalovirus reactivation and mucor infection after transplan-

tation. His AML relapsed with 60% donor chimerism in May 2020. The patient started venetoclax in combination with decitabine as of May 21, 2020. Bone marrow biopsy was planned to be performed after four cycles of venetoclax and decitabine for monitoring disease activity.

Case VI (Table 1)

A 63-year-old female was diagnosed with AML in January 2019. Karyotyping showed 46, XX, t(13;15) (q34;q11.2), der (14) detected in only one produced metaphase. After receiving 3+7 induction chemotherapy with cytarabine and idarubicin, she had a serious anal abscess and persistent minimal residual disease. She received 4 cycles of decitabine but her disease remained refractory. She was then started on azacytidine and venetoclax in August 2019. After the fourth combined treatment cycle, she achieved complete remission. Venetoclax was well tolerated (5 days ramp up: 100; 200; 400 mg), except for grade 3 neutropenia requiring interruptions of venetoclax for 1-2 weeks. The absolute neutrophil count improved after receiving granulocyte colony stimulating factor. She received venetoclax/5-azacytidine for 10 months and remained in molecular remission. The patient is still on treatment with venetoclax plus 5-azacytidine.

Case VII (Table 1)

A 66-year-old male was diagnosed with AML in November 2011. After receiving 3+7 induction therapy with cytarabine and idarubicin, 4 consolidation cycles with high-dose cytarabine (HiDAC) were given which resulted in molecular remission. In April 2013, his disease relapsed and was refractory to 4 cycles of azacytidine. After achieving complete remission with FLAG chemotherapy, he underwent matched-related-allo-SCT in September 2013. His disease relapsed in February 2019 and he received 6 cycles of azacytidine again. He had complete remission again. His disease relapsed in February 2020. He was started on azacytidine in combination with venetoclax (5 days ramp up: 100; 200; 400 mg) in February 2020. He received venetoclax for 2 months along with two cycles of azacytidine. The patient was cytopenic at the initiation of therapy (related to disease). He received venetoclax for two months and he developed persistent grade 4 thrombocytopenia, recurrent pneumonia and cellulitis in dorsum of the foot. Venetoclax had to be stopped. He passed away from hemorrhagic cardiac tamponade in May 2020.

Four of all AML patients (Case II, IV, V and VII) had relapsed disease after allogeneic hematopoietic stem cell transplantation and were unfit for using intensive induction chemotherapy (venetoclax plus HMA). In two of those patients (case IV and V), bone marrow biopsy will be performed after 4 cycles of HMA in combination with venetoclax; in the other two patients venetoclax was not well tolerated and had to be stopped.

The first patient (case II) had grade 2 thrombocytopenia and neutropenia at the initiation of therapy related to disease and received 1 month of venetoclax with grade 4 thrombocytopenia and neutropenia. She developed pneumonia and cytomegalovirus reactivation and had discontinuation of venetoclax. The second patient (case VII) also had grade 4 thrombocytopenia and neutropenia related to disease at the beginning of venetoclax, he developed pneumonia and cellulitis and venetoclax had to be withdrawn.

We also reported on three patients with R/R-AML treated with venetoclax and HMA. Two patients (case III and case IV) achieved complete remission. The first patient (case III) received two months of venetoclax and had complete remission. He developed pneumonia and passed away from sepsis. The second patient (case VI) was treated with venetoclax / 5-azacytidine for 10 months and venetoclax was well tolerated.

One patient (case I) experienced early death within 30 days of therapy. At the initiation of therapy, he had grade 4 thrombocytopenia and required platelet replacement every day. He passed away because of gastrointestinal bleeding.

Discussion

Thanarajasingam et al showed 19% 3-year OS among 351 R/R AML transplated patients [1].

Venetoclax combination with HMA has increasingly been used in the treatment of AML patients. Konopleva et al have reported a phase II study about venetoclax in patients with high-risk R/R-AML or unfit for intensive chemotherapy. They indicated that overall response rate was 19%. Partial bone marrow response and incomplete hematologic recovery has been shown in 19% of the patients. This study declared the efficiency of venetoclax monotherapy for R/R-AML patients [17].

Another large, multicenter, phase 1b study showed favorable response rate to venetoclax in combination with HMA in high-risk groups, such as poor cytogenetics, age 75 or older, secondary AML patients ineligible for intensive chemotherapy. The rate of complete response plus complete response with incomplete hematological recovery was 67% [4].

According to Gaut et al the objective response rate was 35.7% and OS was 4.7 months in R/R-AML patients treated with venetoclax combination (HMA or low-dose cytarabine) therapy [3]. The results of

Table 1. Characteristics of seven patients

Characteristics	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Gender	Male	Female	Male	Female	Male	Female	Male
Age at diagnosis	44	39	44	29	18	62	57
Date at diagnosis	November 2019	March 2019 Seconder AML	September 2019	April 2019	December 2018	January 2019	November 2011
Karyotype at diagnosis	46, XY, del 5q31: 50%, 7q22.1-q22.2 and 7q31.2: 62%	46, XX	46, XY, del 5q31:50%).	46, XX	46, XY	46, XX, t(13;15) (q34;q11.2), der (14)	Failed
Response to induction therapy	MRD+	CR	CR	CR	MRD+	MRD+	CR
Consolidation therapy	Azacytidine (2 cycles)	FLAG	Azacytidine (2 cycle)	FLAG	FLAG	Decitabine (4 cycles)	HDAC (4 cycles)
Response status to consolidation therapy	MRD+	CR	CR	CR	N/A	MRD+	CR
Date of relapse	NA (Persistent MRD)	N/A	December 2019	N/A	N/A (Persistent MRD)	N/A (Persistent MRD)	April 2013
Salvage chemoterapy	Decitabine (1 cycle) +Venetoclax	N/A	Decitabine (2 cycles) +Venetoclax	N/A	N/A	Azacytidine(4 cycles) +Venetoclax	Azacytidine(4cycles), FLAG
Disease status after salvage therapy	N/A	CR	CR	CR	N/A (Persistent MRD)	CR	Hematological CR
Lines of therapy before venetoclax and hypomethylating agents	2	3	2	3	3	2	6
Disease status before venetoclax	MRD+, refractory	Relapsed	Relapsed	Relapsed	Relapsed	Relapsed	Relapsed
Venetoclax start date	April 2020	November 2019	29 January 2020	6 April 2020	The first using date of Venetoclax: 5,11,2019 (for 35 days) The second using date of Venetoclax (after second HCT): 21 May 2020 (for 2 months)	8 August 2019	9 March 2020

Continued on the next page

Characteristics	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Dose of Venetoclax used (mg)	400	400	400	200	400	400	400
Concomitant therapy	Decitabine (1 cycle)	Azacytidine (2 cycles)	Decitabine (2 cycles)	Azacytidine (3 cycles)	Decitabine (2 cycles)	Azacytidine (10 cycles)	Azacytidine (2 cycles)
Response to venetoclax	N/A	N/A	CR	Will be evaluated after fourth course of azacytidine	Will be evaluated after fourth course of decitabine	CR	N/A
Interruption of therapy	N/A	Yes (discontinuation)	N/A	None	None	Yes	N/A
Duration of interruption	N/A	N/A	N/A	None	N/A	Intermittent (for 1-2 weeks)	N/A
CR achieved	N/A	N/A	Yes	Will be evaluated after fourth course of azacytidine	Will be evaluated after fourth course of decitabine	Yes	N/A
Adverse events	Cytopenia	Cytopenia	Cytopenia	Cytopenia	Cytopenia	Cytopenia	Cytopenia
Anemia/grade	Yes/2	Yes/2	Yes/3	Yes/3	No	Yes/1	Yes/2
Neutropenia/grade	Yes/4	Yes/4	Yes/4	Yes/ 4	Yes/4	No	Yes/4
Thrombocytopenia/ grade	Yes/4	Yes/4	Yes/3	Yes/ 4	Yes/4	Yes/4	Yes/4
Febrile neutropenia	Yes	Yes	Yes	Yes	Yes	No	Yes
Infections	Pneumonia	Pneumonia, CMV reactivation	Pneumonia	Recurrent tooth abscess	CMV reactivation, mucor infection	None	Recurrent pneumonia, cellulitis
Disease status at last follow up	Progressive	Progressive, Kloamsa as a salvage chemotherapy	CR	Will be evaluated after fourth course of azacytidine	Will be evaluated after fourth course of decitabine	CR	Progressive
Alive at last follow up	No	No	No	Yes	Yes	Yes	No
Causes of death	GIS bleeding	Sepsis	Sepsis, multiorgan failure	None	None	None	Cardiac tamponade

N/A: Not applicable. 3+7: Idarubicin/Ara-C induction: Idarubicine 12 mg/ m2 daily for 3 days and Cytarabine 100mg/ m2 daily for 7 days. Decitabine: 20 mg/ m2 daily for 5 days every 28 days. Azacytidine: 75 mg/ m2 daily for 7 days every 28 days. FLAG: fludarabine 30 mg/m2/day + Ara-C 2 g/m2 /day (days 1-5) and G-CSF.

venetoclax in combination with HMA or low-dose cytarabine seem to be promising and this treatment will be an alternative option in R/R-AML patients.

Furthermore, TET 2 mutations and mutations in other genes related wıth methylation would be of interest in AML patients under demethylatıng therapy [18].

Intensive therapies for AML are generally not suitable for elderly or patients with comorbidities. In our experience, we have seen that we could provide complete response in R/R AML patients with venetoclax-based treatments. Furthermore, venetoclax-based therapies may be an alternative in patients who are unfit for intensive chemotherapy. These outcomes showed that using venetoclax combined with HMA in R/R-AML should be kept in mind. As predicted by our cases, this might be an alternative salvage option for preventing the use of standard intensive chemotherapies for unfit R/R patients with AML.

Author contributions

Design of the study: Sema Secilmis, Alparslan Merdin, Mehmet Sinan Dal, Fevzi Altuntas
Supervision: Mehmet Sinan Dal, Merih Kizil Cakar, Fevzi Altuntas
Data Collection: Sema Secilmis
Data analysis: Sema Secilmis, Alparslan Merdin, Nuran Ahu Baysal, Mehmet Sinan Dal, Merih Kizil Cakar, Fevzi Altuntas
Literature search: Sema Secilmis, Alparslan Merdin, Nuran Ahu Baysal, Mehmet Sinan Dal, Merih Kizil Cakar, Fevzi Altuntas

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Conflict of interests

The authors declare no conflict of interests.

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