International Journal of Gerontology 17 (2023) 243–246
https://doi.org/10.6890/IJGE.202310_17(4).0006

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Venetoclax-Based Regimen for Elderly Patients with Acute Myeloid Leukemia: A Real-World Experience from a Tertiary Center in Taiwan

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ARTICLE INFO

Accepted 10 March 2023

Keywords:
leukemia, myeloid, acute,
aged,
survival analysis,
venetoclax

SUMMARY

Background: Venetoclax, in combination with a hypomethylating agent or low-dose cytarabine, is approved for the treatment of acute myeloid leukemia (AML) in elderly patients or in those who are ineligible for intensive chemotherapy. The aim of our study was to investigate whether the venetoclax-containing regimen improved the survival of elderly AML patients in Taiwan.
Patients and methods: Thirty-two elderly patients (≥ 60 years) diagnosed with AML at our hospital from January 2018 to October 2022 were retrospectively enrolled. Clinical characteristics and molecular profiles of the patients were captured by chart review. All statistical analyses were calculated by using MedCalc Statistical Software.
Results: The median overall survival (OS) of our entire cohort was 4.0 months (95% confidence interval, 1.13–33.3 months). Patients receiving venetoclax-containing regimens or the best available therapy (BAT) had median OS of 33.3 months and 1.5 months, respectively ($p < 0.001$). The response rate of the venetoclax-containing regimen was 68.8% (11/16). Three patients treated with venetoclax underwent allogeneic peripheral blood stem cell transplantation and remained in remission at the last follow-up. Patients aged 75 years or older who were treated with venetoclax-containing regimens had better survival when compared to those who received BAT (11.3 months vs. 0.4 months, $p = 0.018$). Multivariate analysis showed that elderly AML patients aged 75 years or younger and those receiving venetoclax-containing regimens were 2 independent good prognostic factors for OS.
Conclusion: Venetoclax-based regimens prolonged the survival of elderly AML patients in Taiwan, even in those aged 75 years or older.

1. Introduction

Treatments for elderly patients with acute myeloid leukemia (AML) use to be an unmet medical need. Patients over 60 years old or with comorbidities usually have dismal outcomes because intensive chemotherapy frequently resulted in a high mortality rate. In one retrospective study on AML patients who were ineligible for intensive chemotherapy in Japan, the median survival of these patients treated with azacitidine, low-dose cytarabine (LDAC), or best supportive care was 9.2, 2.2, and 2.2 months, respectively.[1] In another European study, the survival for AML patients aged 70 years or older receiving hypomethylating agents was 9.2 months, and the complete remission rate was 19.7%.[2] There was no difference in response rate and overall survival rates in unfit newly diagnosed AML patients treated with azacitidine or decitabine, according to an analysis from the PATHEMA registry.[3]

Venetoclax is a BH3 mimetic highly selective inhibitor for B-cell leukemia/lymphoma-2 (BCL-2) and can restore the activation of apoptosis in cancer cells.[4] Since 2018, venetoclax in combination with a hypomethylating agent (azacitidine or decitabine), or LDAC, has become a new treatment choice for unfit patients with AML, and their outcome has improved a lot. In a double-blinded randomized trial on AML patients, treatment with azacitidine plus venetoclax extended survival to 14.7 months, compared to 9.6 months with azacitidine alone.[5] The complete remission rate was 66.4%, and the responses were rapid and durable. In a retrospective analysis, intermediate- to high-risk AML patients aged over 60 were able to proceed to hematopoietic stem cell transplantation (HSCT) under remission status, and their survival was not reached.[6] Based on the above evidence, venetoclax, combined with a hypomethylating agent or LDAC, has been used to treat elderly AML patients in Taiwan. This retrospective study aimed to analyze the efficacy and safety of venetoclax-based regimens in elderly AML patients in Taiwan.

2. Patients and methods

From Jan. 2018 to Oct. 2022, 32 patients aged 60 years or older were diagnosed with AML by bone marrow examination at MacKay Memorial Hospital, Taipei, Taiwan, and they were all enrolled. There were 17 patients treated with venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) or LDAC. They received venetoclax with a daily dose of 100–300 mg for 7–28 days per cycle, combined with azacitidine (75 mg/m^2 intravenously/subcutaneously on days 1–7), decitabine (20 mg/m^2

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intravenously on days 1–5), or LDAC (40 mg subcutaneously daily for 5–10 days) until progression, intolerance, or to allogeneic peripheral blood stem cell transplantation (PBSCT). Another 15 elderly AML patients were treated with the best available therapy (BAT) including chemotherapy or best supportive care. Clinical information including complete medical history, laboratory data, computed tomography of the chest and abdomen, positron emission tomography and results of bone marrow study were collected. The protocol of the retrospective cohort study was approved by the Institutional Research Ethics Committee of MacKay Memorial Hospital (20MMHIS442e).

2.1. Statistics

Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or the date of last follow-up. Categorical variables were compared using the Chi-square test or Fisher's exact test. Survival analysis was performed by the Kaplan-Meier method. Prognosticators for survival endpoints, including age, gender, cytogenetic risk, de novo AML, and PBSCT, were assessed by Cox proportional hazards regression model. All statistical tests were two-tailed, with the significance level set at $p < 0.05$. Variables associated ($p < 0.1$) with OS on univariable analyses were included in the multivariable regression model. All analyses were conducted using MedCalc Statistical Software version 20.2 (MedCalc Software bvba, Ostend, Belgium; 2022).

3. Results

3.1. Patient characteristics

From Jan. 2018 to Oct. 2022, thirty-two elderly patients diagnosed with AML were enrolled in this study at our hospital, including 25 (78.1%) with de novo, and 6 (18.8%) secondary to myelodysplastic syndrome. Twenty patients (62.5%) were treatment-naive for their disease at referral to our hospital. The median age was 72 years (range, 61–93 years), with a slightly male predominance (53.1%). Thirty patients had cytogenetic study, and 7 patients had undergone molecular profilings by next-generation sequence (NGS). Twelve patients were in intermediate-II to high cytogenetic risk, according to 2010 ELN risk stratification. Seventeen patients (53.1%) received venetoclax in combination with a hypomethylating agent or LDAC. In these 17 patients treated with venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) or LDAC, venetoclax was given at a daily dose of 100–300 mg for 7–28 days per cycle, azacitidine intravenously/subcutaneously at the dose of 75 mg/m^2 on day 1 to day 7, decitabine intravenously at the dose of 20 mg/m^2 on day 1 to day 5, or LDAC subcutaneously at the dose of 40 mg daily for 5 to 10 days until progression, intolerance, or to allogeneic PBSCT. A median of 3 cycles of venetoclax-based regimen (range, 1–14 cycles) was given to these 17 patients. Another 15 patients received BAT including chemotherapy (n = 8) and best supportive care (BSC) (n = 7). Patients aged 70 years or older tended to receive BSC, and fit patients received chemotherapy regimens including the idarubicin (2 days) plus cytarabine (5 days) regimen or LDAC. Patients in the BAT group were significantly older than those in the venetocalx group, but other characteristics were similar (Table 1). Three patients underwent allogeneic PBSCT, and all of them received venetoclax-containing regimens. The median follow-up time for all patients was 4 months. The median follow-up time for the venetoclax group and BAT group was 33.3 months and 1.5 months, respectively.

3.2. Efficacy, safety, and survival

One patient had an induction death resulting from intracranial hemorrhage, which occurred before treatment initiation. Treatment response for the rest of the 16 patients was accessed, and the complete response (CR)/CR with incomplete count recovery (CRi) rate was 68.8% (11/16). Three patients underwent allogeneic PBSCT under remission status after 2–4 cycles of treatment and remained in remission at the last follow-up. Eight patients in the BAT group received chemotherapy and only one achieved CR. The patient then died of febrile neutropenia one month later.

The median OS was 33.3 months and 1.5 months for patients receiving venetoclax-based regimen or BAT, respectively ($p = 0.0015$) (Figure 1A). There was a significant survival benefit for venetoclax-based regimen in patients aged 75 years or older (11.3 months vs. 0.4 months, $p = 0.018$) (Figure 1B). Univariate analysis revealed that only treatment with the venetoclax-based regimen and age younger than 75 years old were significantly associated with better OS (Table 2). In multivariate analysis, the younger age of 60–74 years and treatment with a venetoclax-based regimen remained to be 2 independent favorable prognostic factors for OS in elderly AML patients (Table 2).

4. Discussion

The efficacy of venetoclax in combination with a hypomethylating agent has been shown in a phase 3 trial comparing azacitidine plus venetoclax with azacitidine plus placebo (VIALE-A).[5] In this study, the OS was significantly longer in the azacitidine-venetoclax group (14.7 months vs. 9.6 months, $p < 0.001$). Venetoclax in combination with a hypomethylating agent or LDAC has become the recommended treatment for elderly patients with untreated AML in

Table 1
Characteristics of the 32 elderly AML patients.

Characteristics	All patients	Venetoclax		*p* value
		With (n = 17)	Without (n = 15)	
Median age (range)	72 (61–93)	71 (61–89)	79 (66–93)	0.014
Gender (%)				1.000
Male	17 (53.1)	9 (52.9)	8 (53.3)	
Female	15 (46.9)	8 (47.1)	7 (46.7)	
Cytogenetic risk* (%)				0.583
Favorable and int-I	20 (62.5)	12 (70.6)	8 (53.3)	
Int-II and adverse	10 (31.2)	4 (23.5)	6 (40)	
Unknown	2 (6.2)	1 (5.9)	1 (6.7)	
Genomic risk† (%)				0.356
Favorable	5 (15.6)	4 (23.5)	1 (6.7)	
Intermediate and adverse	5 (15.6)	3 (17.6)	2 (13.3)	
Unknown	22 (68.7)	10 (58.8)	12 (80)	
FLT3-ITD (%)				0.204
Yes	5 (15.6)	3 (17.6)	2 (13.3)	
No	6 (18.8)	5 (29.4)	1 (6.7)	
Unknown	21 (65.6)	9 (52.9)	11 (80)	
AML (%)				0.147
De novo	25 (78.1)	15 (88.2)	10 (66.7)	
Secondary	7 (21.9)	2 (11.8)	5 (33.3)	
HSCT (%)				0.093
Yes	3 (9.4)	3 (17.6)	0 (0)	
No	29 (90.6)	14 (82.4)	15 (100)	

Abbreviations: AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation.
* Cytogenetic risk according to 2010 ELN recommendations. † 2022 ELN risk stratification by genetics at initial diagnosis.

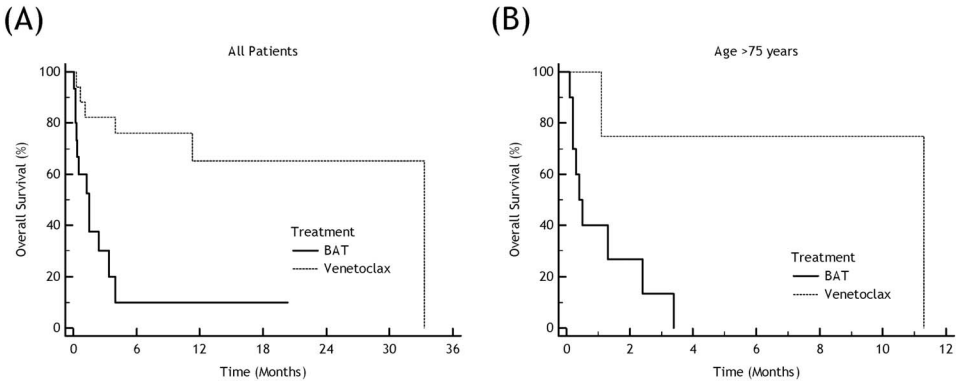

Figure 1. Overall survival (OS) of the 32 elderly patients with AML. (A) OS of all patients: The median OS was 33.3 months and 1.5 months for patients receiving venetoclax-based regimen or BAT, respectively (p = 0.0015). (B) OS of patients aged 75 years or older stratified by treatment: There was a significant survival benefit for venetoclax-based regimen in patients aged 75 years or older (11.3 months vs. 0.4 months, p = 0.018). Abbreviations: BAT: best available therapy.

Table 2
Stepwise multivariate logistic regression models for the association of significant patient characteristics and overall survival.

Factors	Univariate	Multivariate	
	p value	OR (95% CI)	*p* value
Venetoclax	< 0.001	0.20 (0.06–0.64)	0.007
Age < 75 years	0.002	0.27 (0.09–0.78)	0.015
Male	0.085	-	
Favorable cytogenetic risk	0.476		
De novo AML	0.203		
HSCT	0.089	-	

Abbreviations: CI, confidence interval; HSCT, hematopoietic stem-cell transplantation; OR, odds ratio.

both the National Comprehensive Cancer Network and the European Society for Medical Oncology guidelines.

The herein study presented a real-world treatment experience in 32 elderly AML patients at a tertiary medical center in Taiwan. In the BAT group, 15 patients received chemotherapy (n = 8) or best supportive care (n = 7). Their outcome was dismal, with a median OS of 1.5 months. Four patients aged 60 to 74 received intensive chemotherapy, and their OS was 4.0 months, compared to 0.4 months for those treated with LDAC and best supportive care. The difference in outcome in the BAT group might be related to the underlying medical condition of these patients and not necessarily the treatment they received. Only one patient with secondary AML transformed from chronic myeloid leukemia achieved CR after treatment with ponatinib.

On the other hand, 17 patients received venetoclax in combination with a hypomethylating agent or LDAC, and the median OS was 33.3 months. It is noteworthy that our patients received a relatively lower dosage of venetoclax ranging from 100 mg daily for 7 days to 300 mg daily for 28 days per cycle. This was mainly because venetoclax was not reimbursed by the National Health Insurance Administration of Taiwan for most of the patients. In the VIALE-A study, patients in the azacitidine-venetoclax arm received 400 mg of venetoclax daily for 28 days per cycle. In our study, patients aged 75 years or older treated with a venetoclax-based regimen had significantly better survival when compared to those treated with BAT. Despite a lower dosage of venetoclax use in our patients, our subgroup analysis still observed a better OS in these patients.

In the present study, 12 patients aged 60 to 74 received a venetoclax-based regimen. Seven patients achieved CR after 1–2 cycles of treatment, and 5 patients had either induction death (n = 1) or refractory diseases (n = 4). The median OS was 33.3 months, compared to 4.0 months for patients receiving intensive chemotherapy. Two patients were still in remission after 4 and 5 cycles of treatment, respectively, and one of them had an NPM1 mutation without FLT3-ITD. A retrospective study reported that the median OS of patients with a median age of 72 years was 381 days.[7] Another study in Japan reported that the median OS of elderly AML patients (median age of 77.5 years, range 68–85 years) was not reached at a median follow-up of 16.3 months.[8] In our study, three patients with intermediate- to high-risk AML underwent allogeneic PBSCT under remission status and were still alive without relapse at the last follow-up. A retrospective study including AML patients aged 60 years or more showed that the OS for PBSCT patients was not reached at a median follow-up of 24.1 months.[6] Our study supported the use of a venetoclax-based regimen as a bridging therapy for elderly AML patients to PBSCT.

Due to the retrospective nature of this study, some limitations are present. First, patients were treated with various venetoclax-based and chemotherapy regimens using different dosing schedules. This might have affected the outcomes of these patients. Second, because of the relatively small sample size in this study and a very short follow-up time in the BAT group, the interpretation of the statistical results should be cautious. Despite the presence of the above-mentioned limitations, the real-world experiences reported here suggested that venetoclax may be a promising treatment option for elderly patients with AML in Taiwan.

5. Conclusions

Our study reported a real-world experience of a venetoclax-based regimen compared with BAT for elderly AML patients in Taiwan. Venetoclax, combined with a hypomethylating agent or LDAC, significantly improved OS, and it could bridge intermediate- to high-risk elderly AML patients to receive SCT after achieving CR.

Conflicts of interest

We declare that there are no conflicts of interest relevant to this study.

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