Treatment outcomes and safety of reduced-dose venetoclax plus antifungal agents to treat acute myeloid leukemia: A single hospital experience in Taiwan

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Abstract. Venetoclax, an orally administered B-cell lymphoma 2 inhibitor, requires dose adjustments when coadministered with cytochrome P450 inhibitors in patients with acute myeloid leukemia (AML). The present study retrospectively analyzed data on progression-free survival (PFS), overall survival (OS) and drug-related adverse events in patients with AML who received adjusted low-dose venetoclax with antifungal agents, compared with those receiving conventional chemotherapy regimens (I3A7, LDAC, and I2A5) , at a single hospital. In total, 45 patients with AML who were treated between January 2015 and December 2021 were retrospectively included. A significantly longer median OS time was observed in the group receiving idarubicin [12 mg/m^2 intravenous (IV) on days 1-3] and cytarabine (100 mg/m^2 continuous IV infusion on days 1-7) (I3A7 group) (median not reached) compared with that in the venetoclax group [10.7 months; 95% confidence interval (CI), 6.3-20.8], the low-dose cytarabine (LDAC) group (4.7 months; 95% CI, 0.8-18.7) and the group receiving idarubicin (12 mg/m^2 IV on days 1-2) with cytarabine (100 mg/m^2 continuous IV infusion on days 1-5) (I2A5 group) (2.3 months; 95% CI, 0.5-2.3). Similarly, the median PFS time was significantly longer in the I3A7 group (29.0 months; 95% CI, 1.1-29.0) compared with that in the venetoclax (8.0 months; 95% CI, 0.8-10.8), LDAC (2.1 months; 95% CI, 0.1-6.4) and I2A5 (0.9 months; 95% CI, 0.1-4.7) groups. Grade 3 or higher adverse hematological events were common across all treatment groups. Cardiovascular events and grade 3 or higher tumor lysis syndrome occurred only in the venetoclax group (14 and 7%, respectively). In conclusion, low-dose venetoclax combined with antifungal agents appears to be less effective than standard treatment but superior to both LDAC and the I2A5 treatment regimens. Venetoclax also demonstrates a relatively low infection risk. However, careful monitoring for cardiovascular events and tumor lysis syndrome during venetoclax administration is crucial, particularly in patients with relevant medical histories.

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Introduction

Venetoclax, an orally administered B-cell lymphoma (BCL-2) inhibitor plays a crucial role in regulating cell survival by inhibiting apoptosis. Overexpression of BCL-2 in cancer cells can promote the survival and proliferation of such cells (1-4). Venetoclax selectively binds to BCL-2, restoring the apoptotic process within cancer cells and inhibiting tumor growth (5). Studies have demonstrated the notable therapeutic efficacy of venetoclax in various malignancies, including acute myeloid leukemia (AML), chronic lymphocytic leukemia, multiple myeloma and mantle cell lymphoma (6-20).

In hematological-oncological treatment, antifungal agents are commonly used either for therapeutic or prophylactic purposes alongside anticancer medications (21). Specific antifungal agents, such as posaconazole and voriconazole, act as cytochrome P450 inhibitors (22,23), and since venetoclax is metabolized through cytochrome P450, their co-administration can result in drug interactions, necessitating a reduction in venetoclax dosage to prevent potential adverse effects (24).

The literature emphasizes the need for dose adjustments when combining venetoclax with cytochrome P450 inhibitors

in patients with AML. However, drug interactions affecting venetoclax blood concentrations are non-linear (25,26). Currently, research on clinical outcomes in patients with AML receiving reduced venetoclax doses due to such interactions is limited. Furthermore, venetoclax has a restricted duration of coverage under Taiwan's National Health Insurance system. Therefore, to alleviate the financial burden or extend treatment duration, combining venetoclax with antifungal agents may be a viable option for patients with AML who cannot tolerate intensive chemotherapy.

This single-center study retrospectively investigated progression-free survival (PFS), overall survival (OS) and drug-related adverse events (AEs) in patients with AML who received adjusted venetoclax doses in combination with antifungal agents compared with those receiving standard treatment.

Materials and methods

This retrospective observational single-center study included patients who had been treated within a 7-year period between January 2015 and December 2021, and who met the following inclusion criteria: i) Age >20 years; ii) diagnosis of non-M3 AML classified according to the French-American-British classification system (27); iii) AML treatment with venetoclax and a cytochrome P450 inhibitor (posaconazole or voriconazole); iv) induction therapy with idarubicin + cytarabine and high-dose cytarabine consolidation therapy; and v) treatment with low-dose cytarabine (LDAC). Patient demographic and clinical characteristics, namely age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (28), cytogenetic risk category (29), somatic mutations, bone marrow blast count, PFS, OS and optimal treatment response dose, were collected retrospectively. Ethical approval was granted by the Chi-Mei Medical Center Institutional Review Board (approval no. 11107-L01) on August 2, 2022, and the study commenced on August 8, 2022, and was conducted in accordance with the Helsinki Declaration. The requirement for informed patient consent was exempted by the Institutional Review Board. Patients were enrolled from the Division of Hematology-Oncology, Department of Internal Medicine, Chi-Mei Medical Center (Tainan, Taiwan). To ensure patient confidentiality, all data were anonymized and were accessible only through unique codes. In accordance with legal regulations, only the principal investigator was authorized access and allowed to manage the complete dataset.

The primary outcomes of the study were OS (defined as the time from the start of drug treatment to death) and PFS (defined as the time from treatment initiation to disease progression or treatment change). For patients alive at the study endpoint, data were based on the most recent confirmation of survival date.

Secondary outcomes included the evaluation of treatment-related grade 3/4 AEs, based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 (30), and treatment response rates, based on the criteria outlined by Döhner *et al* (31).

AML treatment regimens included induction therapy with idarubicin and cytarabine (12 mg/m^2 idarubicin on days 1-3 + 100 mg/m^2 cytarabine on days 1-7 or 12 mg/m^2 idarubicin on days 1-2 + 100 mg/m^2 cytarabine on days 1-5). Consolidation therapy involved 1-2 g/m^2 cytarabine on days 1, 3 and 5. Venetoclax-based regimens included 100 mg venetoclax on days 1-28 + 300 mg posaconazole on days 1-28 + 100 mg azacitidine on days 1-7 (28 days per cycle) or 100 mg venetoclax on days 1-28 + 300 mg posaconazole on days 1-28 or 20 mg/m^2 LDAC on days 1-10 + 100 mg venetoclax on days 1-28 + 300 mg posaconazole on days 1-28 or 200 mg voriconazole twice daily on days 1-28 (28 days per cycle). The cytarabine-based regimen involved 20 mg/m^2 LDAC on days 1-10 (28 days per cycle). Treatment continued until disease progression or until the patient could no longer tolerate drug side effects.

Statistical analysis. Statistical analysis involved descriptive statistics to analyze retrospective patient data. Baseline clinical characteristics were compared among the four groups using appropriate statistical methods. Age was analyzed using the Kruskal-Wallis test, as it did not follow a normal distribution. Categorical variables were analyzed using the Fisher-Freeman-Halton Exact Test. The overall response rate and AEs were also analyzed using the Fisher-Freeman-Halton Exact Test to assess statistical differences across groups. Associations with OS and PFS were assessed using a Cox proportional hazards regression model. The Kaplan-Meier product-limit method was used to calculate PFS and OS curves, with differences between subgroups assessed using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference. All analyses were performed using MedCalc version 20.007 (MedCalc Software Ltd.) or R software version 4.4.2 (The R Foundation for Statistical Computing).

Results

Patients. Between January 2015 and December 2021, 45 patients with AML were retrospectively included in the study. These patients were stratified into the following four groups based on their first-line treatment regimen: The I3A7, LDAC and I2A5 groups, which received conventional chemotherapy as standard therapy, and the venetoclax group, which received an adjusted low-dose venetoclax regimen combined with antifungal agents. The I3A7 group were those patients who received idarubicin on days 1-3 + cytarabine on days 1-7 (n=19); the venetoclax group included patients who received one of the three venetoclax-based regimens, namely venetoclax + azacitidine + antifungal agents, venetocalx + LDAC + antifungal agents or venetocalx+antifungal agents (n=14). All patients in the venetoclax group received 100 mg venetoclax daily alone with antifungal agents. The LDAC group received 20 mg/m^2 LDAC on days 1-10 (n=9); and the I2A5 group were those who received idarubicin on days 1-2 + cytarabine on days 1-5 (n=3). Demographic characteristics are summarized in Table I, and the groupings are illustrated in Fig. 1. In the I3A7 group, the median age was 52 years (range, 46-75 years), with only 1 patient (5%) older than 75 years. In the venetoclax group, the median age was 71 years (range, 50-82 years), with 5 patients (36%) older than 75 years. In the LDAC group, the median age was 79 years (range, 71-90 years), with 7 patients (78%) older than 75 years. In the I2A5 group, the median age was

Table I. Baseline demographic and clinical characteristics of the study patients.

Characteristic	I3A7 group (n=19)	Venetoclax group (n=14)	LDAC group (n=9)	I2A5 group (n=3)	P-value
Age, years					<0.01
Median (range)	52 (46-75)	71 (50-82)	79 (71-90)	69 (36-79)	
≥75, n (%)	1 (5)	5 (36)	7 (78)	1 (33)	
Sex					0.88
Male, n (%)	10 (53)	7 (50)	6 (67)	2 (67%)	
ECOG performance status score, n (%)					0.17
0	11 (58)	6 (43)	2 (22)	1 (33)	
1	7 (37)	8 (57)	4 (44)	2 (67)	
2	1 (5)	0 (0)	3 (33)	0 (0)	
Bone marrow blast count, n (%)					0.34
<30%	14 (74)	6 (43)	7 (78)	2 (67)	
30-50%	2 (11)	2 (14)	1 (11)	1 (33)	
>50%	3 (16)	6 (43)	1 (11)	0 (0)	
Cytogenetic risk category, n (%)					0.80
Favorable	4 (21)	2 (14)	0 (0)	0 (0)	
Intermediate	12 (63)	11 (79)	8 (89)	3 (100)	
Poor	3 (16)	1 (7)	1 (11)	0 (0)	
Somatic mutations, n (%)					0.12
ASXL1	1 (5)	0 (0)	0 (0)	0 (0)	
BCR ABL1	0 (0)	0 (0)	1 (11)	0 (0)	
CBFB-MYH11	0 (0)	2 (14)	0 (0)	0 (0)	
FLT3&NPM1	1 (5)	0 (0)	1 (11)	0 (0)	
IDH2	0 (0)	1 (7)	0 (0)	0 (0)	
NPM1	2 (11)	0 (0)	0 (0)	0 (0)	
RUNX1 CBFB-MYH11	3 (16)	0 (0)	0 (0)	0 (0)	
TP53	1 (5)	1 (7)	0 (0)	0 (0)	
abn(17p)	1 (5)	0 (0)	0 (0)	0 (0)	
del(5q)	1 (5)	0 (0)	0 (0)	0 (0)	

I3A7, idarubicin (12 mg/m² IV on days 1-3) plus cytarabine (100 mg/m² continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m² IV on days 1-2) plus cytarabine (100 mg/m² continuous IV infusion on days 1-5); LDAC, low-dose cytarabine; ECOG, Eastern Cooperative Oncology Group.

69 years (range, 36-79 years), with 1 patient (33%) older than 75 years. Regarding sex distribution, 10 patients (53%) in the I3A7 group, 7 patients (50%) in the venetoclax group, 6 patients (67%) in the LDAC group, and 2 patients (67%) in the I2A5 group were male. Most patients (58%) in the I3A7 group had an ECOG performance score of 0, while most patients in the other groups had a performance status score of 1. Bone marrow blast counts were predominantly <30% across all groups. The cytogenetic risk category was mostly intermediate, and somatic mutations were most prevalent in the I3A7 group.

Baseline clinical characteristics showed a statistically significant age difference across the four groups (P<0.01). However, no significant differences were found for sex (P=0.88), ECOG (P=0.17), bone marrow blast count (P=0.34), cytogenetic risk category (P=0.80) or somatic mutations (P=0.12) (Table I). Additionally, age was found to be significantly associated with OS (P<0.05), but no significant association was found for PFS (Table SI).

Efficacy. The primary OS outcomes are shown in Fig. 2. The I3A7 group was found to have a significantly longer median OS time (median not reached) compared with the venetoclax + antifungal group [10.7 months; 95% confidence interval (CI), 6.3-20.8], the LDAC group (4.7 months; 95% CI, 0.8-18.7) and the I2A5 group (2.3 months; 95% CI, 0.5-2.3). For PFS, the I3A7 group had a significantly longer median PFS time (29.0 months; 95% CI, 1.1-29.0) compared with the venetoclax group (8.0 months; 95% CI, 0.8-10.8), the LDAC group (2.1 months; 95% CI, 0.1-6.4) and the I2A5 group (0.9 months; 95% CI, 0.1-4.7) (Fig. 3). The response rates of all the study patients are detailed in Table II, with a statistically significant difference in overall response rate observed across the groups (P<0.05). In the

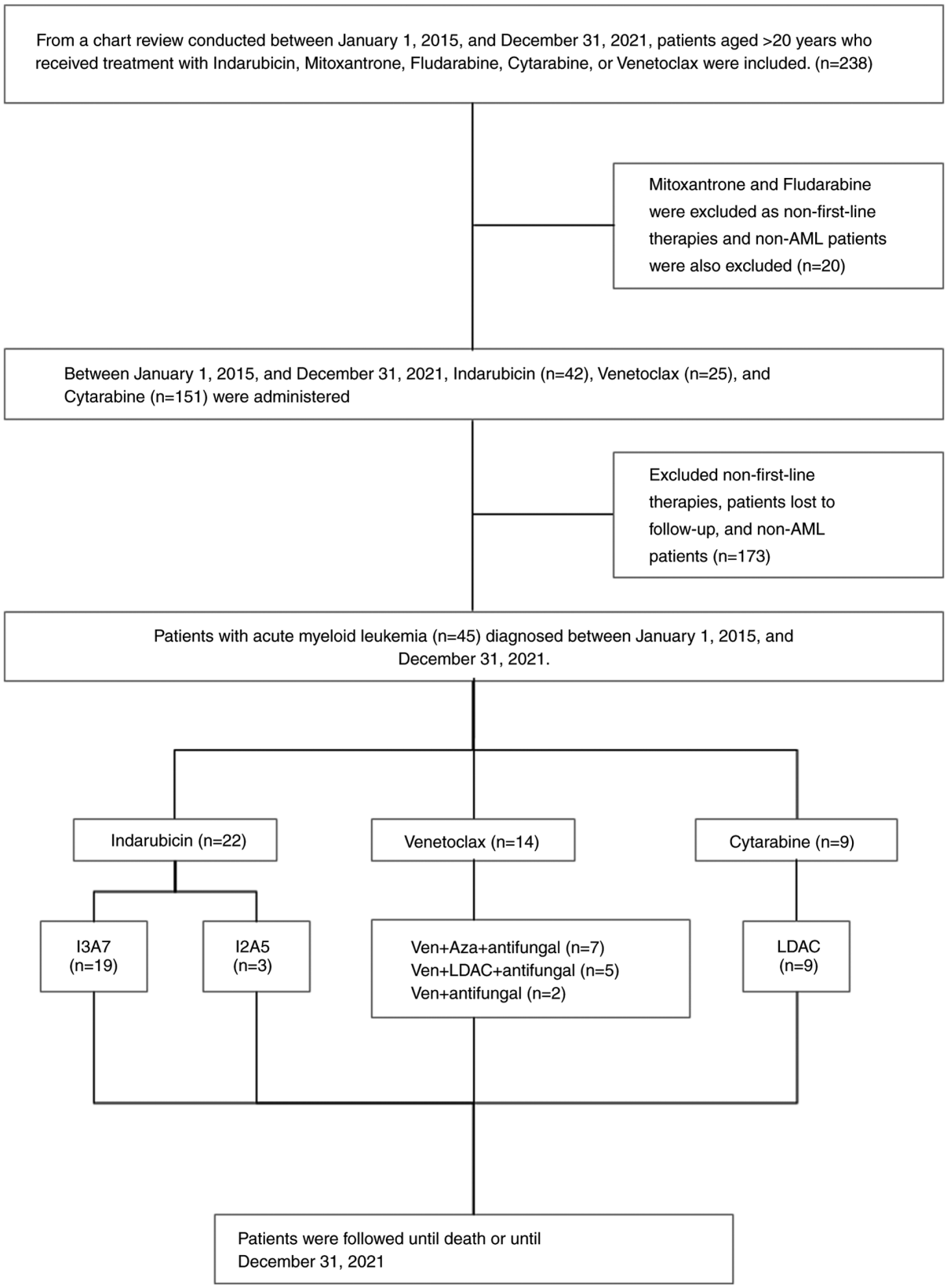

Figure 1. AML treatments in the study cohort. Aza, azacitidine; I3A7, idarubicin (12 mg/m^2 IV on days 1-3) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m^2 IV on days 1-2) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-5); LDAC, low-dose cytarabine; Ven, venetoclax.

I3A7 group, 4 patients (21%) achieved complete remission, while 4 patients (21%) also achieved complete remission, but with incomplete hematological recovery. In the venetoclax group, 1 patient (7%) achieved complete remission with incomplete hematological recovery. Partial response was observed in 2 patients in both the venetoclax (14%) and I2A5

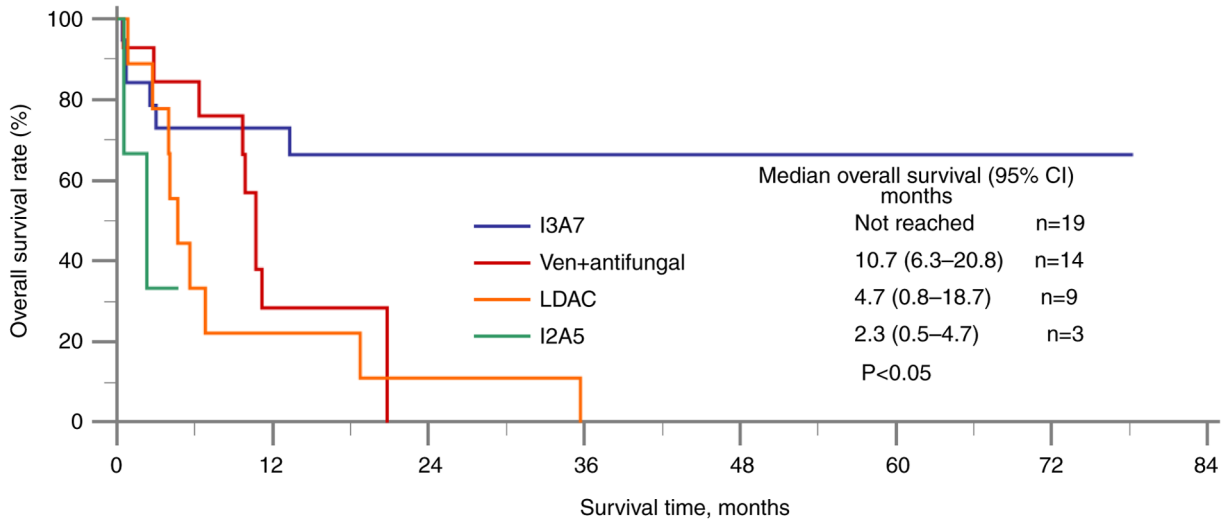

Figure 2. Overall survival outcomes in each group. I3A7, idarubicin (12 mg/m² IV on days 1-3) plus cytarabine (100 mg/m² continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m² IV on days 1-2) plus cytarabine (100 mg/m² continuous IV infusion on days 1-5); LDAC, low-dose cytarabine; Ven, venetoclax.

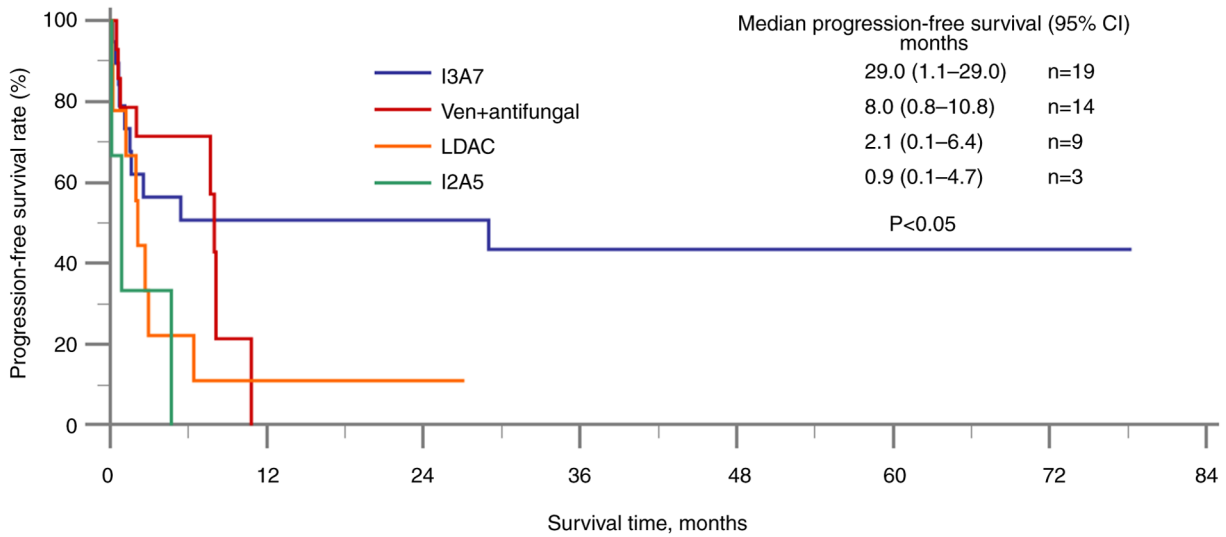

Figure 3. Progression-free survival outcomes in each group. I3A7, idarubicin (12 mg/m² IV on days 1-3) plus cytarabine (100 mg/m² continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m² IV on days 1-2) plus cytarabine (100 mg/m² continuous IV infusion on days 1-5); LDAC, low-dose cytarabine; Ven, venetoclax.

(67%) groups. Stable disease was reported in 6 patients (32%) in the I3A7 group, 6 patients (43%) in the venetoclax group and 3 patients (33%) in the LDAC group. Progressive disease occurred in 5 patients (26%) in the I3A7 group, 5 patients (36%) in the venetoclax group, 6 patients (67%) in the LDAC group and 1 patient (33%) in the I2A5 group. Among the patients treated with venetoclax with antifungal agents, those who also received azacitidine had a longer median OS time (20.8 months; 95% CI not reached) compared with those who received LDAC (6.3 months; 95% CI, 2.8-10.7) (Fig. 4). Patients receiving venetoclax, antifungal agents and azacitidine had a longer median PFS time (10.8 months; 95% CI not reached) compared with those receiving venetoclax, antifungal agents and LDAC (2.0 months; 95% CI, 0.6-2.0) (Fig. 5). Additionally, patients in the I3A7 group exhibited a longer median RFS time (not reached) compared with those in the venetoclax plus antifungal agents group (2.4 months, 95% CI: NA) (Fig. S1). However, none of these differences were statistically significant.

Safety. The safety analysis comprised 45 patients (19 in the I3A7 group, 14 in the venetoclax group, 9 in the LDAC group and 3 in the I2A5 group), with the most common AEs summarized in Table III. Grade 3 or higher hematological AEs were frequently reported in the groups, including thrombocytopenia (89, 71, 78 and 67% in the I3A7, venetoclax, LDAC and I2A5 groups, respectively), neutropenia (100, 79, 67 and 100%, respectively) and anemia (37, 57, 44 and 67%, respectively). No statistically significant differences in AEs were observed among the groups, including anemia, neutropenia, thrombocytopenia, fever, sepsis, increased ALT levels, pneumonia, other infections, increased AST levels, increased Scr levels, cardiovascular events and tumor lysis syndrome. Grade 3 or higher infection-related AEs were most frequently reported

Table II. Response rates for all patients.

Response	I3A7 group (n=19)	Venetoclax group (n=14)	LDAC group (n=9)	I2A5 group (n=3)	P-value
CR, n (%)	4 (21)	0 (0)	0 (0)	0 (0)	
CRi, n (%)	4 (21)	1 (7)	0 (0)	0 (0)	
PR, n (%)	0 (0)	2 (14)	0 (0)	2 (67)	
SD, n (%)	6 (32)	6 (43)	3 (33)	0 (0)	
PD, n (%)	5 (26)	5 (36)	6 (67)	1 (33)	
ORR, n (%)	8 (42)	3 (21)	0 (0)	2 (67)	P<0.05

CR, complete remission; Cri, complete remission with incomplete hematological recovery; I3A7, idarubicin (12 mg/m^2 IV on days 1-3) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m^2 IV on days 1-2) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-5); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; LDAC, low-dose cytarabine.

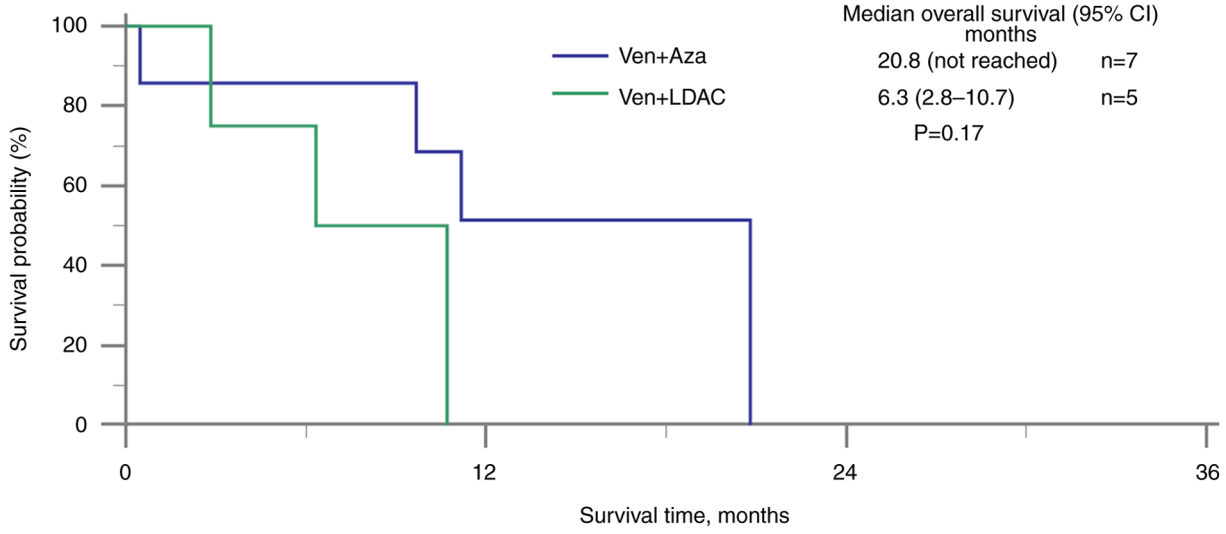

Figure 4. Overall survival outcomes in the venetoclax subgroups. Aza, azacitidine; LDAC, low-dose cytarabine; Ven, venetoclax.

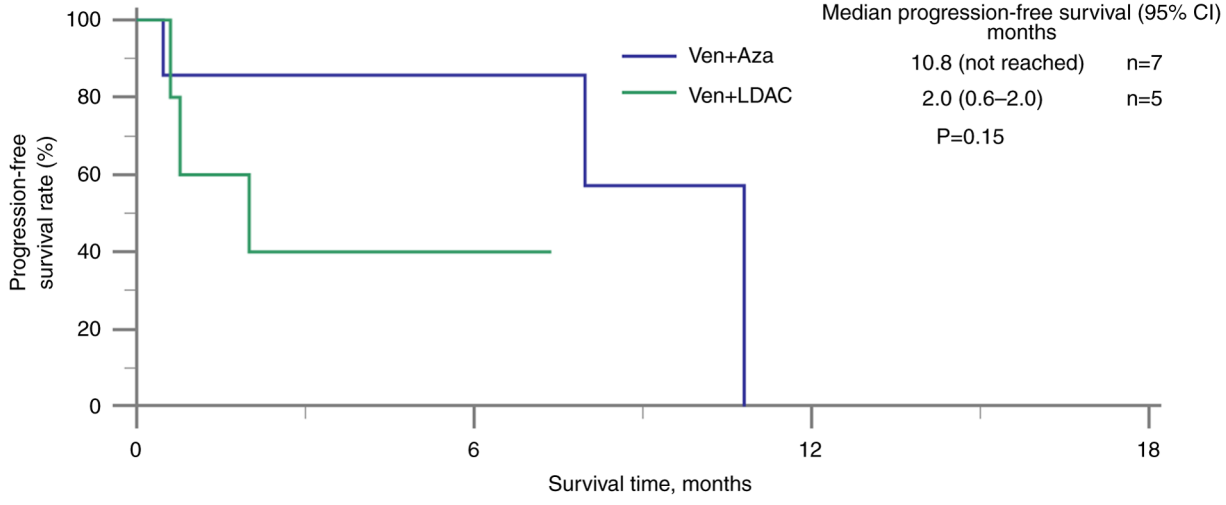

Figure 5. Progression-free survival outcomes in the venetoclax subgroups. Aza, azacitidine; LDAC, low-dose cytarabine; Ven, venetoclax.

in the I3A7 group and included fever (21, 7, 0 and 0%, in the I3A7, venetoclax, LDAC and I2A5 groups, respectively), pneumonia (11, 21, 33 and 33%, respectively), sepsis (63, 36, 11 and 67%, respectively) and other infections (21, 14, 22 and

Table III. Patient AEs.

	I3A7 group (n=19)		Venetoclax group (n=14)		LDAC group (n=9)		I2A5 group (n=3)		
Event	All grades	≥ Grade 3	All grades	≥ Grade 3	All grades	≥ Grade 3	All grades	≥ Grade 3	P-value
All AEs	19 (100)	19 (100)	14 (100)	13 (93)	9 (100)	8 (89)	3 (100)	3 (100)	>0.99
Anemia	18 (95)	7 (37)	12 (86)	8 (57)	8 (89)	4 (44)	3 (100)	2 (67)	0.85
Neutropenia	19 (100)	19 (100)	12 (86)	11 (79)	7 (78)	6 (67)	3 (100)	3 (100)	0.16
Thrombocytopenia	19 (100)	17 (89)	13 (93)	10 (71)	8 (89)	7 (78)	3 (100)	2 (67)	0.39
Fever	13 (68)	4 (21)	6 (43)	1 (7)	5 (56)	0 (0)	3 (100)	0 (0)	0.27
Pneumonia	2 (11)	2 (11)	3 (21)	3 (21)	3 (33)	3 (33)	1 (33)	1 (33)	0.41
Sepsis	12 (63)	12 (63)	5 (36)	5 (36)	2 (22)	1 (11)	2 (67)	2 (67)	0.14
Other infections	5 (26)	4 (21)	6 (43)	2 (14)	4 (44)	2 (22)	0 (0)	0 (0)	0.51
AST increased	8 (42)	1 (5)	5 (36)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	0.12
ALT increased	10 (53)	1 (5)	8 (57)	0 (0)	1 (11)	0 (0)	1 (33)	0 (0)	0.11
Scr increased	5 (26)	2 (11)	7 (50)	1 (7)	4 (44)	0 (0)	0 (0)	0 (0)	0.33
CV event	0 (0)	0 (0)	2 (14)	2 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0.26
TLS	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0.58

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CV, cardiovascular; I3A7, idarubicin (12 mg/m^2 IV on days 1-3) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-7); I2A5, idarubicin (12 mg/m^2 IV on days 1-2) plus cytarabine (100 mg/m^2 continuous IV infusion on days 1-5); Scr, serum creatinine; TLS, tumor lysis syndrome; LDAC, low-dose cytarabine.

0%, respectively). Finally, cardiovascular events and grade 3 or higher TLS (14 and 7%, respectively) were only observed in the venetoclax group.

Discussion

For elderly patients with AML or those unfit for intensive chemotherapy, venetoclax combined with hypomethylating agents or LDAC has become the gold-standard treatment in numerous clinical settings (13,15). However, in Taiwan, financial constraints and limited health insurance coverage restrict the widespread clinical application of this treatment approach. During the period covered by the present study, venetoclax was not reimbursed under Taiwan's National Health Insurance system. According to current regulations, its coverage is restricted to frail patients and limited to a maximum of four cycles. As a result, patients requiring venetoclax must bear a portion of the medication cost themselves. Considering that not all patients have the financial capacity to afford the treatment, a potential solution to this issue is using a reduced dosage of venetoclax in conjunction with antifungal agents, which can lower medication costs while maintaining efficacy and safety. This approach aims to optimize treatment outcomes while alleviating the financial burden on patients.

Elderly patients with AML often have reduced tolerance to intensive chemotherapy and face an increased risk of complications. Consequently, low-intensity treatment regimens are advisable to balance efficacy and tolerability. Previous research has highlighted that advanced age is associated with a poorer prognosis in AML, emphasizing the need to consider physiological age and overall health when making treatment decisions (32). Although no statistically significant differences were observed in the cytogenetic risk categories (P=0.80) and somatic mutations (P=0.12) across treatment groups in our study (which may reflect the small sample size or patient heterogeneity), these factors remain important prognostic markers in AML (33) and should be considered in future studies that aim to tailor treatment strategies more effectively.

The present study uniquely focused on the efficacy and safety of reduced-dose venetoclax (primarily 100 mg daily) combined with antifungal agents such as voriconazole and posaconazole. In this retrospective analysis, the I3A7 group demonstrated superior OS and PFS times compared with the venetoclax, LDAC and I2A5 groups, consistent with current AML treatment guidelines (34). Additionally, among the patients receiving venetoclax combined with antifungal agents, those treated with azacitidine exhibited numerically longer median OS and PFS times compared with those treated with LDAC. While this trend suggests a potential benefit of combining azacitidine with venetoclax over LDAC , the differences were not statistically significant. The I3A7 group also demonstrated a numerically longer median RFS time compared with the venetoclax plus antifungal agents group, although this analysis was limited to patients achieving complete remission (8 in the I3A7 group and 1 in the venetoclax group), reducing the statistical power and with a lack of statistically significant differences, thereby limiting the generalizability of the findings. Larger studies are needed to validate these results and explore venetoclax-based regimens in AML treatment. While the venetoclax group exhibited slightly lower OS and PFS times than the I3A7 group, patients also experienced fewer hematological and infection-related AEs. Additionally, despite poorer survival outcomes compared with the more intensive I3A7 chemotherapy regimen, venetoclax achieved more favorable outcomes than traditional treatments

such as LDAC and I2A5, particularly when combined with hypomethylating agents. Patients in the venetoclax group also exhibited a lower risk of infection compared with the I3A7 and I2A5 groups, and patients who were treated with hypomethylating agents showed better survival outcomes than those treated with the LDAC regimen. Accordingly, venetoclax-based combination regimens should be considered a superior treatment option to LDAC or I2A5, particularly for elderly or frail AML patients.

Regarding antifungal prophylaxis, 3 patients in the I3A7 group and 7 patients in the LDAC group did not receive prophylactic antifungal therapy. However, no cases of fungal infections were observed in any treatment group throughout the study. This aligns with recent findings (35) that suggest a low incidence of invasive fungal infections among patients with AML treated with venetoclax and hypomethylating agents, even without routine antifungal prophylaxis. This study (35) and others, suggest that while antifungal prophylaxis can be beneficial, its necessity should be determined based on individual patient risk factors and specific treatment regimens. Similarly, another previous study (36) found that antifungal prophylaxis did not significantly reduce fungal infections in patients receiving azacitidine alone, further indicating that routine prophylaxis may not be necessary for all patients. These findings imply that the risk of fungal infections in certain AML treatment regimens may be lower than expected, and the decision to implement antifungal prophylaxis should be tailored to the specific treatment context and patient risk profile. The present clinical observations, supported by the extant literature, suggest that the absence of antifungal prophylaxis in specific patient groups, including the LDAC group, did not lead to an increased incidence of fungal infections. In the venetoclax group, antifungal agents were, in fact, primarily administered to increase drug concentration not to prevent infections.

The observed statistical difference in overall response rate ($P<0.05$) in the present study provides valuable insights into the clinical implications of the treatment regimens. This finding suggests that certain regimens may have better efficacy, but their safety profiles should still be carefully evaluated to ensure a favorable risk-benefit balance. By contrast, no statistically significant differences in AEs were observed among the groups. However, common hematological toxicities, including anemia, neutropenia and thrombocytopenia, remain critical concerns in AML treatment and necessitate careful monitoring and supportive care, such as transfusions when required. Similarly, infection-related events, including fever and sepsis, should be actively managed through early detection and prophylactic strategies to mitigate potential complications. While hepatic and renal toxicities did not differ significantly between groups, routine liver and kidney function assessments remain essential in clinical practice. While no statistically significant differences in AEs were found, continued monitoring remains essential to ensure patient safety and optimize treatment outcomes.

Notably, in the venetoclax group, two grade 3 or higher cardiovascular AEs were identified. Literature regarding venetoclax-related cardiovascular reactions is limited (12,14,20), with only one such publication suggesting a potential mechanism where venetoclax induces cardiovascular toxicity through the NF-κB and BCL-2 pathways, which regulate oxidative stress-mediated cardiac inflammation and apoptosis (37). However, further analysis is needed to better understand the origins of these adverse cardiovascular reactions.

Another grade 3 or higher adverse reaction identified in the present study was TLS, with incidence rates comparable to those reported in previous clinical trials (11,12,20). Venetoclax is metabolized by the liver enzyme cytochrome P450 3A4 (24), therefore the present study conducted a subgroup analysis in the venetoclax group to assess the combined effects of multiple cytochrome P450 (CYP) inhibitors and chemotherapy drugs on OS and PFS time. However, the analysis concluded that this did not significantly influence OS or PFS time, which suggests that a 75% reduction in venetoclax dosage with CYP inhibitors may not affect treatment efficacy (24). This dose reduction could potentially lower medication costs and reduce adverse reactions compared with normal doses of venetoclax. Previous studies have shown that strong CYP inhibitors such as ritonavir (38), ketoconazole (39), itraconazole (26,40,41) and posaconazole (25,42) can significantly increase venetoclax levels in the bloodstream.

The unique aspect of the present study was the use of low-dose venetoclax in combination with potent CYP inhibitors. Compared with standard chemotherapy, the venetoclax plus antifungal agents regimen resulted in lower PFS time, OS time and overall response rate. However, it also had a lower infection risk and reduced drug costs, offering potential savings for patients.

The present study also had several limitations primarily stemming from its retrospective design, which may have resulted in small sample sizes in certain groups, potentially introducing statistical bias. For instance, the venetoclax plus azacitidine and antifungal agents group was not represented separately in Figs. 1-4 due to the small sample size, which limited the statistical power for meaningful comparisons. However, aggregated data for this subgroup showed promising trends in terms of efficacy and safety. While these findings are encouraging, they should be interpreted with caution, and further studies with larger sample sizes are necessary to validate these observations. Moreover, venetoclax blood concentrations were not monitored during the study period, although it has previously been suggested that body surface area is negatively correlated with venetoclax levels, implying that monitoring these blood concentrations could improve personalized treatment strategies (43). A final limitation of the present study is the absence of patients with relapsed AML and those receiving standard venetoclax therapy, which is a key area for future research.

In conclusion, the present study suggests that low-dose venetoclax combined with antifungal agents may be inferior to standard chemotherapy treatment, but more effective than regimens involving LDAC or I2A5. In addition, venetoclax demonstrated a relatively low risk of infection, but vigilant monitoring for adverse cardiovascular events and TLS, particularly in patients with relevant medical histories, is crucial. Further studies are necessary to validate these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SYH and KYW were responsible for designing the research and extracting the data. WTH, CYL and KYC conducted the statistical analysis and handled data visualization and interpretation. TSW contributed to data analysis and interpretation, particularly in assessing statistical outcomes and refining subgroup classifications. SYH and TSW prepared the initial draft of the manuscript, performed critical revisions to the manuscript, focusing on essential intellectual content and reviewed the data analysis. TSW shaped the study's conclusions and aligned them with the statistical findings. SYH and TSW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki guidelines and received approval from the Ethics Committee of Chi Mei Medical Center, Liouying (Tainan, Taiwan; approval no. 11107-L01). The requirement for informed patient consent was exempted by the Institutional Review Board.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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