RESEARCH LETTER

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TO THE EDITOR:

Cardiac events in patients with acute myeloid leukemia treated with venetoclax combined with hypomethylating agents

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Venetoclax, a small-molecule inhibitor of B-cell lymphoma-2, in combination with the hypomethylating agents (HMA) azacitidine or decitabine, is FDA-approved for elderly/unfit patients with acute myeloid leukemia (AML). It is frequently used both in the upfront and relapsed/refractory setting based on superior efficacy and improved survival of the combination regimen compared with HMA alone.[1]

Cardiac events have been previously described among patients with AML treated with HMA.[2] Treatment with azacitidine was associated with atrial fibrillation (3% to 5%), congestive heart failure (3% to 11%), and a single case of sudden cardiac death reported in phase I-II trials[3-7] in addition to pericarditis and pericardial effusion in the European Product Information. Decitabine has also been associated with myocarditis and reversible cardiomyopathy.[8,9] Less is known about cardiac events in patients with AML treated with the combination of HMA and venetoclax. The VIALE-A study, which compared azacitidine plus venetoclax to azacitidine plus placebo in elderly/unfit patients with AML, included patients ineligible for standard induction chemotherapy due to congestive heart failure (requiring treatment or with an ejection fraction [EF] $\leq$50%) and those with chronic stable angina. In that study, the only cardiac event reported as a serious adverse event was atrial fibrillation, noted in 5% of patients receiving azacitidine plus venetoclax, vs 1% in the azacitidine plus placebo group.[1] Another study of decitabine plus venetoclax in patients with AML ineligible for standard induction therapy (n = 168) reported a single instance of grade 3 cardiac ischemia.[10] Cardiac events in patients with chronic lymphocytic leukemia treated with venetoclax are also rare; a phase II study described atrial fibrillation in 6% of patients and 1 instance of cardiopulmonary failure.[11] Therefore, our objective was to provide a comprehensive description of all cardiac events that occurred in patients with AML undergoing treatment with HMA in combination with venetoclax. Additionally, we sought to determine clinical or genetic factors that might serve as predictors of such events.

All patients with AML who received venetoclax plus HMA treatment at Mayo Clinic sites outside the context of a clinical trial between November 2018 and November 2020 were retrospectively recruited following Mayo Clinic institutional review board approval. Patients received venetoclax plus HMA either in the upfront or relapsed/refractory setting; however, relapses after allogeneic stem cell transplant were excluded.

Cardiac events were defined as any cardiac complication occurring while treatment was ongoing. This included newly diagnosed cardiac disease, such as congestive heart failure or development of acute coronary syndrome. It also included patients with a change in baseline cardiac status, such as a patient with known heart failure with reduced EF (HFrEF) who experienced a further decrease in left ventricular EF (LVEF) while on treatment. Chronic, stable cardiac disease, such as in a patient with known HFrEF who tolerated treatment without LVEF decrease or symptomatic exacerbation, was not classified as a cardiac event.

A total of 170 consecutive patients of median age 69 years (range 17-91), with 63% males, were studied, of whom 64% (109/170) received venetoclax plus HMA as upfront therapy. Of the 61 patients with

Submitted 15 February 2022; accepted 9 March 2022; prepublished online on *Blood Advances* First Edition 31 March 2022; final version published online 12 September 2022. DOI 10.1182/bloodadvances.2022007333.

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The full text version of this article contains a data supplement.

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Table 1. Cardiac event details, including timing and management among 34 patients with acute myeloid leukemia treated with HMA and venetoclax, stratified by pretreatment EF

Cardiac events	All patients with cardiac events	Patients with EF <50%	Patients with EF ≥50%
Patients with cardiac event, no. (%)	34 (20)	10 (31)	24 (22)
Total number of cardiac events	48	18	30
Venetoclax cycle during cardiac event, no. (%)			
1	15 (44)	5 (50)	10 (42)
2	9 (26)	1 (10)	8 (32)
3	4 (12)	1 (10)	3 (13)
>Cycle 3	6 (18)	3 (30)	3 (13)
Cardiac event subtype, no. (%)			
LVEF decrease	10 (21)	8 (44)	2 (7)
Troponin elevation	7 (15)	4 (22)	3 (10)
Presumed type II, anemia Hb<8	*3/7*	*2/4*	*1/3*
Presumed type II, afib with RVR	*1/7*	*0/4*	*1/3*
Unexplained by other factors	*3/7*	*2/4*	*1/3*
Type I NSTEMI	3 (6)	1 (6)	2 (7)
Worsening HFpEF by echo	4 (8)	0 (0)	4 (12)
Cardiogenic pulmonary edema	3 (6)	0 (0)	3 (10)
Atrial fibrillation with RVR	8 (17)	2 (11)	6 (20)
Other symptomatic arrhythmia	4 (8)	2 (11)	2 (7)
Worsening CAD	1 (2)	0 (0)	1 (3)
Pericardial effusion/pericarditis	3 (6)	0 (0)	3 (10)
Cardiopulmonary arrest	2 (4)	0 (0)	2 (7)
Worsening RV dysfunction by echo	3 (6)	1 (6)	2 (7)
Predisposing factors in patients with cardiac events			
Prior cardiac history, no. (%) *	23 (68)	9 (90)	14 (58)
Cardiovascular risk factors (no. of patients)	30 (88)	9 (90)	21 (88)
subtype, no.			
HTN	22	5	17
HLD	15	6	9
Diabetes mellitus	12	2	10
Obesity	10	3	7
Tobacco use	7	3	4
Management of cardiac event, no. (%)			
Outpatient management	4 (12)	0 (0)	4 (17)
Hospital ward admission	21 (62)	7 (70)	14 (58)
ICU/CICU admission	9 (27)	3 (30)	6 (25)
Initiation of new medication	26 (77)	8 (80)	18 (75)
Procedural intervention	2 (6)	1 (10)	1 (4)
Impact of cardiac events on AML therapy, no. (%)			
Venetoclax + HMA discontinued	7 (21)	4 (40)	3 (13)
Venetoclax + HMA interrupted	9 (27)	4 (40)	5 (21)

Note: because most (23/25) events were concurrent, denominators in Predisposing Factors, Management, and Impact sections are number of patients rather than number of events.

CAD, coronary artery disease; cardiogenic pulmonary edema, pulmonary edema seen on imaging, presumed cardiac source, without echo to confirm EF changes; CICU, cardiac intensive care unit; HLD, hyperlipidemia; HTN, hypertension; ICU, intensive care unit; NSTEMI, non-ST elevation myocardial infarction; other symptomatic arrhythmia, arrhythmia other than atrial fibrillation with RVR; RV, right ventricle; troponin elevation, changing troponins without ECG changes.

* Prior cardiac disease by subtype: CAD (n = 10); atrial fibrillation/flutter (n = 9); HFrEF (n = 4); HFpEF (n = 7); aortic/mitral stenosis (n = 6); peripheral arterial disease (n = 1); pericarditis (n = 1); pulmonary edema (n=1).

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Table 2. Comparison of clinical and laboratory characteristics of patients with AML treated with HMA plus venetoclax stratified by occurrence of cardiac events

All patients (n = 170)	Cardiac complication (n = 34)	No cardiac complication (n = 136)	*P*
Patient characteristics			
Median age at venetoclax, y (range)	69 (18-92)	71 (40-91)	.09
Age at venetoclax >60 y, no. (%)	29 (85)	107 (79)	.63
Male gender, no. (%)	21 (62)	86 (63)	1.0
Cardiovascular risk factors, no. (%)	30 (88)	126 (93)	.3
Pretreatment EF <50%, no. (%)	10/32 (31)	24/109 (22)	.29
Median counts at diagnosis (range)			
Hemoglobin, g/dL	8.6 (6.9-13.6)	8.4 (4.8-14)	.22
Leukocyte count, $\times 10^9$/L	4.4 (0.5-112)	3.7 (0.1-145)	.37
Platelet count, $\times 10^9$/L	51 (5-239)	57 (7-444)	.73
AML subdiagnosis, no. (%)			.62
AML, de novo	18 (53)	70 (51)	
AML, post-MDS	10 (29)	49 (36)	
AML, therapy-related	6 (18)	17 (13)	
Venetoclax treatment setting, no. (%)			
Upfront	23 (67)	86 (63)	.69
Relapsed/refractory	11 (33)	50 (37)	
HMA type, no. (%)			.62
Azacitidine	16 (47)	47 (35)	
Decitabine	18 (53)	89 (65)	
Karyotype, no. (%) 2017 ELN risk stratification			.17
Favorable	3 (9)	4 (3)	
Intermediate	14 (41)	68 (50)	
Adverse	17 (50)	64 (47)	
Genomics, no. (%)			
DNMT3A/TET2/ASXL1	16 (47)	49 (36)	.23
DNMT3A	2 (6)	19 (14)	.38
TET2	10 (30)	22 (16)	.08
ASXL1	7 (21)	20 (15)	.43
FLT3	5 (15)	16 (12)	.56
CEBPA	4 (12)	3 (2)	.03
TP53	10 (30)	34 (25)	.51
EZH2	1 (3)	7 (5)	1
IDH2/IDH1	4 (12)	25 (18)	.68
WT1	1 (3)	6 (4)	1
RUNX1	5 (15)	23 (17)	1
SRSF2	3 (9)	21 (15)	.58
NPM1	6 (18)	16 (12)	.38
Median overall survival, mo (95% CI)	6 (3-17)	16 (10-24)	<.001

relapsed/refractory AML, 11 (18%) experienced cardiac events, 10 of whom had received prior anthracycline therapy, and 3 of them had anthracycline-related cardiomyopathy. European Leukemia Net (ELN) risk categorization was either adverse (48%, n = 82) or intermediate (48%, n = 82) in most patients.[12] One hundred forty-one patients (83%) underwent a baseline echocardiogram prior to therapy. Azacitidine 75 mg/m^2 (days 1-7) or decitabine 20 mg/m^2 (days 1-5) was administered with venetoclax for 28 days, with dose adjusted due to concomitant azole use unless noted otherwise (supplemental Table 1).

Forty-eight cardiac events were documented in 34 (20%) patients, 11 of whom (32%) had >1 event; in these 11 patients, 23 of 25 events were concurrent rather than recurrent (Table 1; supplemental Table 1). Eighteen of 48 (38%) cardiac events occurred in the setting of concurrent infection. Cardiac event rates were similar despite

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treatment setting or HMA used: 23/109 (21%) in patients treated upfront vs 11/61 (18%) in the relapsed setting ($P = .46$) and 16/34 (47%) treated with azacitidine vs 18/34 (53%) treated with decitabine ($P = .62$). The most frequent events included a symptomatic decrease in LVEF on echocardiography (21%, n = 10) with median LVEF decrease of 14%, atrial fibrillation with rapid ventricular response (RVR) (17%, n = 8), followed by troponin elevation without electrocardiogram changes (15%, n = 7). Among the 7 patients with troponin elevation, 4 experienced events in the setting of another inciting factor such as severe anemia, whereas the remainder represented a troponin elevation without another explanation (Table 1). Other cardiac events included worsening heart failure with preserved EF (HFpEF) (n = 4), non–atrial fibrillation arrhythmia (n = 4), and pericardial effusion or pericarditis (n = 3). Notably, 2 patients experienced a fatal cardiopulmonary arrest (Table 1). Per Common Terminology Criteria for Adverse Events version 5.0 grading criteria, 37% (n = 18/48) of events were grades 1 to 2, with 44% (n = 21/48) being grades 3 to 4 and 19% (n = 9/48) being grade 5.

Of the 34 patients experiencing cardiac events, 11 (32%) patients had no known preexisting cardiac disease. Moreover, 4 patients (12%) had no known cardiovascular risk factors (Table 1). In regard to timing of cardiac complications, most patients were early in treatment course, with 44% (n = 15), 26% (n = 9), and 12% (n = 4) in cycles 1, 2, and 3, respectively (Table 1). Three of 34 (9%) patients experienced cardiac events between cycles 4 and 6, and only 3 patients experienced cardiac events after cycle 6 during cycles 7, 12, and 22, respectively. Complete details on each of the 34 patients experiencing cardiac events, including type, timing, blood counts at event, and disease status of AML, are elaborated in supplemental Table 1. These events had a significant impact on AML therapy. Approximately half of patients either interrupted (27%) or discontinued (21%) treatment with HMA plus venetoclax due to the cardiac event (Table 1). Furthermore, most (89%) events required inpatient care, of whom a sizable proportion were admitted to the intensive care unit (27%, n = 9). Cardiac management included initiation of new cardiac medications (77%, n = 26), whereas 2 patients required emergency procedural intervention. Unfortunately, the cardiac event itself was fatal in 9 patients (27%) (supplemental Table 2).

Next, we compared patients who experienced cardiac events vs those without cardiac complications and found no significant differences in terms of age (median age, 69 vs 71 years; $P = .09$), ELN risk category (adverse 50% vs 47%, intermediate 41% vs 50%, favorable 9% vs 3%; $P = .17$), cardiovascular risk factors (88% in patients with cardiac events vs 93% in those without events; $P = .30$), disease setting (upfront in 67% of patients with events vs 63% of patients without events; $P = .69$), or type of HMA ($P = .62$) (Table 2). The incidence of *ASXL1*, *TET2*, and *DNMT3A* mutations associated with clonal hematopoieses (*ASXL1* 21% vs 15%; $P = .43$; *TET2* 30% vs 16%; $P = .08$; *DNMT3A* 6% vs 14%; $P = .38$) were similar. A higher incidence of *CEBPA* mutations was noted among patients with cardiac events (12% vs 2%; $P = .03$), which is of unclear significance. In the 141 patients with pretreatment echocardiogram, 31% (10/32) of patients with EF <50% experienced a cardiac complication vs 22% (24/109 patients) of patients with EF ≥50% ($P = .29$).

Our study cohort was followed for a median of 14 months (range, <1-101 months), with 96 deaths (56%). Patients who experienced cardiac events had shortened overall survival of 6 months (range, 3-17) compared with patients without events at 16 months (range, 10-24) ($P < .001$) (Table 2).

Finally, we compared cardiac complication rates in the current study with a previously published Mayo Clinic cohort of 58 elderly patients with AML who were treated with HMA alone.[13] Cardiac events occurred in 5 of the patients who received HMA treatment, including cardiogenic pulmonary edema (n = 2), atrial fibrillation with RVR (n = 2), worsening HFpEF (n = 1), and pericardial effusion (n = 1). Notably, all 5 patients had one or more cardiovascular risk factors; 3 of these patients also had established cardiac disease. It is to be noted that a higher incidence of cardiac events occurred among patients treated with HMA plus venetoclax compared with HMA alone (20% [n = 34] vs 9% [n = 5]; $P = .04$) despite the former cohort being younger (median age, 68 vs 78 years; $P < .0001$).

In summary, this is the first report to illustrate the spectrum of cardiac events encountered in patients with AML treated with HMA in combination with venetoclax; most events occurred early in the treatment course, required inpatient care, and impacted therapy for AML. Our findings regarding a higher incidence of cardiac complications among patients with AML treated with HMA plus venetoclax are not simply reflective of the rate of cardiac complications in older adults because we compared cardiac event rates to elderly AML patients receiving HMA alone. Despite the HMA-alone cohort being older than the HMA plus venetoclax cohort, events rates were lower with HMA monotherapy. Moreover, 38% of cardiac events in the HMA plus venetoclax cohort occurred in the setting of neutropenic fever or infection, pointing to myelosuppression associated with the regimen. The current study is limited by the single-institution retrospective design, and baseline echocardiogram was not obtained in all patients. Taken together, our observations, which warrant validation in multicenter, prospective real-world studies, suggest the importance of cardiac monitoring in patients with AML receiving venetoclax in combination with HMA.

Contribution: I.M.J., E.D.B., K.M., and N.G. designed the study; I.M.J. and F.F. performed research; I.M.J. analyzed data and wrote the paper; and K.M., A.A.-K., H.B.A., K.B., M.R.L., W.J.H., M.V.S., M.M.P., and A.T. provided data and editorial support.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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