

To the editor:

Ventricular arrhythmias and sudden death in patients taking ibrutinib

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Ibrutinib, approved by the US Food and Drug Administration (FDA), is an inhibitor of Bruton tyrosine kinase (BTK).¹⁻⁵ Ibrutinib use is associated with atrial fibrillation (AF), with an incidence of 5% to 6% after 18 months on therapy^{4,6} and up to 16% with longer follow-up.^{2,7} Prompted by an episode of unexplained ventricular tachycardia (VT) in a patient taking ibrutinib, we hypothesized that ibrutinib use may be associated with ventricular arrhythmias (VAs). To further investigate, we gathered 4 cases of VAs in ibrutinib-treated patients, mined the FDA Adverse Event Reporting System (FAERS) for additional reports of VAs in patients receiving ibrutinib, and estimated incidence rates of VAs in clinical trials of ibrutinib.

Individual patients were enrolled on data collection protocols approved by institutional review boards or collected from publicly available data. We obtained adverse events (AEs) for ibrutinib reported to the FAERS from the fourth quarter of 2013 (ibrutinib was approved by the FDA in November 2013) to the fourth quarter of 2015. Additional details were requested for AE reports with the following preferred search terms: ventricular arrhythmia, ventricular fibrillation (VF), Brugada syndrome, right bundle branch block, cardiac arrest, cardiac death, cardiac fibrillation, cardiorespiratory arrest, conduction disorder, sudden death, sudden cardiac death, ventricular extrasystoles, and ventricular tachycardia. If dates of ibrutinib discontinuation, cardiac events, or death were redacted, we used the date when the patient was last seen alive or when the event was filed. Patients for whom there was not enough information to determine the timing of ibrutinib administration or for whom ibrutinib was discontinued before the event were excluded. Clinical trial data were drawn from published results. Median time on therapy was assumed to be mean time on therapy to calculate total time on therapy for the group of interest. Statistical analysis was performed by using STATA 14 (STATA, College Station, TX).

Our index patient was a 60-year-old man who had chronic lymphocytic leukemia (CLL) and no prior cardiac history. He was a vigorous exerciser with resting sinus bradycardia. Two months after beginning ibrutinib, he reported new palpitations. He experienced syncope 86 days after initiating ibrutinib. Frequent premature ventricular contractions (PVCs) and nonsustained VT were identified (Figure 1A). An exercise stress test was negative for ischemic changes, but polymorphic VT occurred when he transferred from stretcher to treadmill (Figure 1B). Cardiac catheterization and echocardiogram were normal. Electrophysiologic studies induced PVCs originating from the moderator band but could not ablate the focus; therefore, he was started on antiarrhythmics and a cardioverter-defibrillator was implanted. Ibrutinib was resumed at discharge. Attempted downtitration

of his quinidine later resulted in an increase in PVCs. He has since been maintained on ibrutinib, quinidine, and metoprolol for 28 months with occasional nonsustained VT on device interrogation. A second patient was a 55-year-old man with refractory CLL, primary sclerosing cholangitis, and no prior cardiac disease. He had a witnessed collapse 366 days after initiating ibrutinib and was resuscitated. While he was hospitalized, he had an R-on-T phenomenon resulting in polymorphic VT followed by VF. Defibrillation restored sinus rhythm. Coronary angiography, echocardiogram, cardiac magnetic resonance imaging, and genetic testing for inherited sodium channelopathies all failed to identify any cardiac abnormalities. A third patient was a 53-year-old man with CLL, AF, coronary artery disease, and a 30-pack-year smoking history. Nineteen days after initiating ibrutinib, he reported palpitations and presyncope. Holter monitoring showed frequent ventricular ectopic beats. Nine days later, he was found to have polymorphic VT (Figure 1C). A fourth instance of VF while taking ibrutinib may have been triggered by an acute ischemic event. Ibrutinib was stopped for all patients; in 3 patients, ibrutinib was resumed 10 to 50 days later; two patients had recurrent VAs (details are provided in supplemental Table 1, available on the *Blood* Web site).

We queried the FAERS for cases of VAs or sudden death in patients taking ibrutinib. This database contains AEs submitted by health care professionals, consumers, and manufacturers. We analyzed the preferred terms listed above, and further limited our study population to patients without concomitant acute illness. We identified 7 additional instances of VT/VF and 6 sudden deaths (supplemental Table 1). Ten of 13 patients had no prior cardiac history. No patients were taking other medications known to induce cardiac arrhythmias. For all patients, the median time to event from ibrutinib initiation was 65 days (range, 6-698 days) and the median age was 61 years (range, 49-85 years). In all patients identified in the FAERS database who underwent additional cardiac workup, no clear cause could be identified.

In published clinical trials of ibrutinib that enrolled approximately 1000 total participants, we identified 10 cases of sudden death or cardiac arrest (Table 1). Incidence rates of sudden death as a function of time on therapy were calculated. The weighted average of the incidence rates was 788 events per 100 000 person-years. In comparison, rates of sudden cardiac death for 65-year-olds are in the range of 200 to 400 events per 100 000 person-years,⁸⁻¹¹ which were exceeded in all but 1 of the ibrutinib studies. Four studies (RESONATE,³ RESONATE-2,⁵ HELIOS,¹² and RAY¹³) had control arms that did not contain ibrutinib, but only the HELIOS study publicly reported all grade 3 to 5 AEs, which allowed for direct comparison of incidence

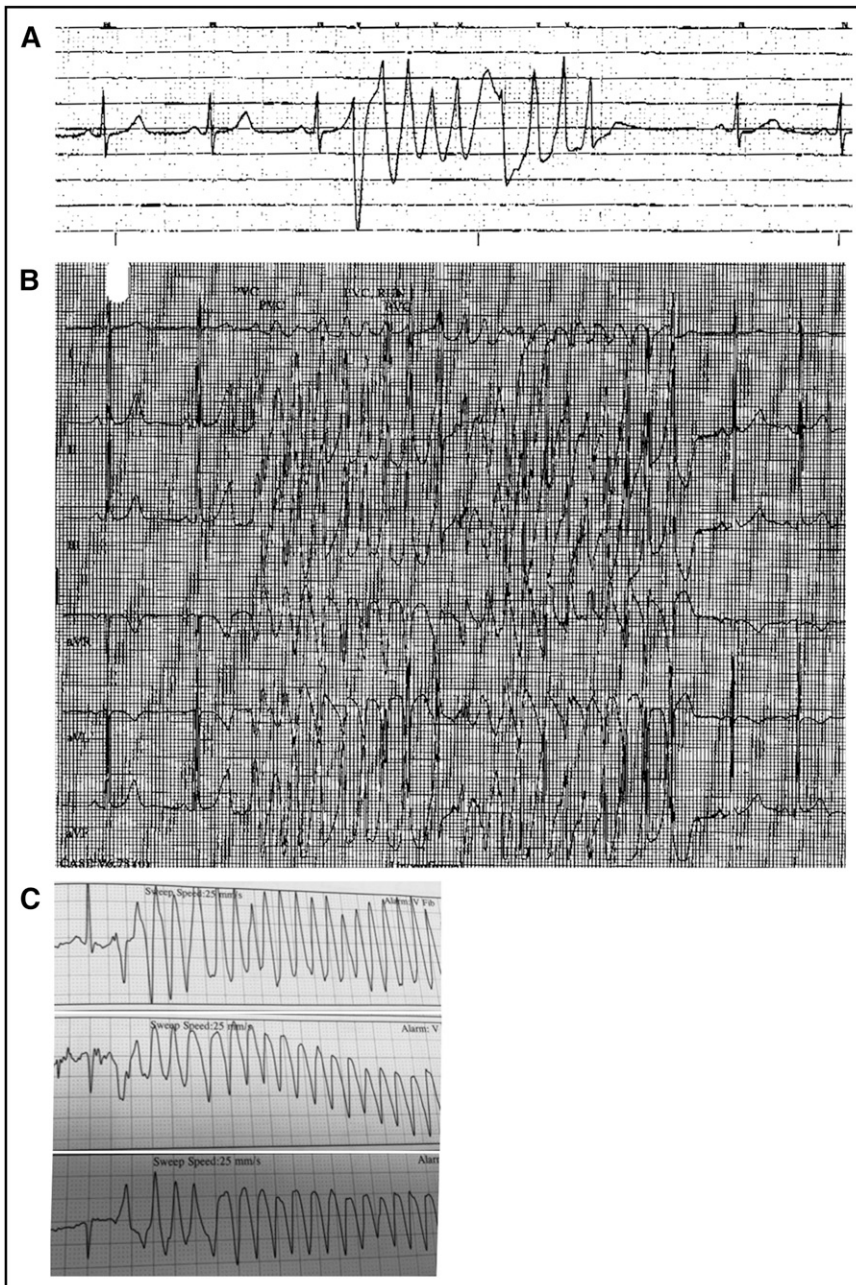


Figure 1. Ventricular tachycardia captured in patients on ibrutinib. (A) A brief run of nonsustained ventricular tachycardia is seen on telemetry shortly after a syncopal episode in a patient who had been taking ibrutinib 420 mg per day for 86 days. (B) A 20-beat run of polymorphic ventricular tachycardia experienced by the same patient with syncope while receiving ibrutinib. (C) Polymorphic ventricular tachycardia identified in a patient reporting presyncope after 28 days receiving ibrutinib 420 mg per day.

rates between 2 randomized populations. The aggregate number of grade ≥ 3 VAs, cardiac arrests, and sudden deaths in HELIOS was 7 in the ibrutinib-containing arm and 0 in the placebo-containing arm (supplemental Table 2). Assuming these events happened in separate patients, this corresponds to 1,991 events per 100 000 person-years versus 0 events per 100 000 person-years, respectively (exact two-sided $P = .025$).

Ibrutinib is an arrhythmogenic molecule, although the arrhythmogenic mechanism is not well understood. A prior study has shown no effect of ibrutinib on QTc length,¹⁴ and patients with monitoring at the time of the event did not display a prolonged QTc (Figure 1). In cultured cardiomyocytes, ibrutinib triggers abnormal action potentials (both early and delayed afterdepolarizations) and increases late sodium current (I_{NaL}), ultimately leading to enhanced automaticity.¹⁵ The kinase responsible for these changes is unknown and may not be BTK¹⁶; ibrutinib inhibits 19 kinases with a half maximal inhibitory concentration (IC_{50}) < 100 nM.¹⁷

In randomized trials to date, any increased risk of VAs or sudden death has been outweighed by the benefits of treating the underlying disease, as shown by the improvement in overall survival in RESONATE³ and RESONATE-2.⁵ However, it is unknown whether this favorable risk-benefit balance will be maintained as ibrutinib treatment is expanded to populations that may be older, have more underlying cardiac disease, or have lower-risk CLL. For example, a case of VT has been reported in a trial examining ibrutinib in asymptomatic early-stage CLL,¹⁸ and 2 recent case reports identified VT in ibrutinib-treated patients with a history of AF¹⁹ and cardiomyopathy.²⁰ In addition, ibrutinib studies currently have short follow-up, and the risk-benefit ratio may change with extended therapy.⁴ Our study is limited by its retrospective approach, the self-reported nature of FAERS data, and lack of access to primary trial data. Not all studies of ibrutinib have reported sudden deaths,²¹ and focusing only on studies that report sudden deaths may overestimate their incidence. Nevertheless, future

Table 1. Ibrutinib studies with reported sudden deaths/cardiac arrests

Studies*	No. of Patients	Median time on therapy (months)	Age (y)		No. of sudden deaths/cardiac arrests in ibrutinib arm	Incidence per 100 000 patient-years (95% CI)	Reference
			Median	Range			
OSU experience: NCT01105247, NCT01217749, NCT01589302, NCT01578707 (RESONATE)	308	20	65	26-91	1	194.8 (4.9-1085.4)	22
NCT01722487 (RESONATE-2)	135	17.4	73	65-89	2	1021.7 (123.7-3690.8)	5
MDACC experience: NCT01105247, NCT01520519, NCT01752426, NCT01578707 (RESONATE)	127	13	61	36-83	2	1453.7 (176.1-5252.1)	23
NCT01500733 (Phase 2 NHLBI)	51	24†	62	33-82	1	980.4 (24.8-5462.4)	24
Swedish Compassionate Use	95	10.2†	69	42-86	1	1238.4 (31.4-6899.9)	25
NCT01611090 (HELIOS)	287	14.7	64	31-86	3	853.3 (176.0-2493.7)	12

CI, confidence interval; MDACC, MD Anderson Cancer Center; NHLBI, National Heart, Lung, and Blood Institute; OSU, The Ohio State University.

*Some of these long term follow-up studies report on patients from the same trials, but they report only on nonoverlapping sets of patients treated at the home institution.

†Median follow-up time. Median time on therapy was not provided.

trials of ibrutinib should report VAs and sudden deaths. Whether more specific BTK inhibitors might mitigate these concerns ultimately depends on whether the cause is attributable to on-target BTK or off-target non-BTK inhibition. Meanwhile, clinicians should inquire about symptoms of VAs in ibrutinib-treated patients, have a low threshold for cardiac workup if they are present, and consider the possibility of VAs when weighing the risk-benefit ratio of ibrutinib therapy.

The online version of this article contains a data supplement.

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Contribution: B.L.L. and J.R.B. conceived and designed the study; all authors collected and/or analyzed data, drafted and provided critical review of the manuscript, and provided final approval of the manuscript.

Conflict-of-interest disclosure: J.R.B. served as a consultant for Gilead Sciences, Infinity Pharmaceuticals, Janssen Pharmaceuticals, Pharmacyclics, Roche/Genentech, Astra-Zeneca, and Abbvie. J.A.J. served as a consultant for Gilead Sciences, Janssen Pharmaceuticals, Pharmacyclics, AbbVie, and Genentech. E.D.J. served as a consultant for Pharmacyclics, Janssen Pharmaceuticals, and Infinity Pharmaceuticals. J.C.B. received institutional research support and served as a consultant for Pharmacyclics, AbbVie, and Gilead Sciences. V.B. served as a consultant for Gilead Sciences, Janssen Pharmaceuticals, Lundbeck, and AbbVie. R.J.G. received institutional research support from AstraZeneca, Kowa American, Novartis, and Pfizer Pharmaceuticals. J.J.M. served as a consultant for Pharmacyclics. The remaining authors declare no competing financial interests.

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To the editor:

More than 1 *TP53* abnormality is a dominant characteristic of pure erythroid leukemia

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Pure erythroid leukemia¹ (PEL), or AML-M6b, is a rare form of leukemia characterized by proliferation of >80% undifferentiated or pronormoblastic immature cells committed exclusively to the erythroid lineage.² Previous reports have described the aggressive nature of erythroid/myeloid leukemia or AML-M6a (acute erythroid leukemia [AEL]) and PEL, as well as their association with high-risk biological features,³⁻¹⁰ including high frequency of *TP53* mutations in up to 53% of patients with AEL.¹¹ Despite these advances, the rarity of PEL has so far limited the ability to define its clinical and biological characteristics. Description of the mutational landscape and clinical outcomes of patients with PEL compared with AEL is therefore needed.

We evaluated all patients with newly diagnosed erythroleukemia treated at The University of Texas MD Anderson Cancer Center from 1980 to 2016. Informed consent was obtained according to protocols approved by the institutional review board in accordance with the Declaration of Helsinki. A diagnosis of AEL was considered if >50% of bone marrow nucleated cells were of erythroid lineage and >20% of nonerythroid cells were blasts.^{2,12,13} Diagnosis of PEL was established if >80% bone marrow nucleated cells consisted of immature erythroid precursors^{2,13-15} or if bone marrow core biopsy or aspirate clot was composed of sheets of immature undifferentiated blasts positive for glycophorin A.^{9,10,16-18} In patients evaluated from 2013 to 2016, whole-bone marrow DNA was subject to a 28- or 53-gene targeted polymerase chain reaction-based next-generation sequencing platform¹⁹ (available in the data supplement on the *Blood* Web site).

Twenty-seven (14%) of 189 patients with erythroleukemia met diagnostic criteria for PEL. Median age was 67 years (range, 33-85 years), with male predominance (ratio 2:1). Patients presented with mean hemoglobin of 8.7 g/dL (range, 8.2-9.2 g/dL), platelets of $25 \times 10^9/L$ (range, $17-32 \times 10^9/L$) and leukocyte count of $3 \times 10^9/L$ (range, $2.2-3.9 \times 10^9/L$). Eleven patients (41%) had therapy-related AML, and 11 (41%) had an antecedent hematologic malignancy, including myelodysplastic syndrome in 10 and chronic myeloid leukemia in 1 patient. Eleven patients (41%) received induction chemotherapy, 9 (33%) hypomethylating agents (HMAs), and 1 (4%) a monoclonal antibody. Six patients (22%) did not receive therapy and

died before treatment initiation. Detailed descriptions of individual patient characteristics are shown in supplemental Tables 1-3.

Cytogenetic analysis was available in 26 (96%) and 147 patients (91%) with PEL and AEL, respectively, and revealed higher frequency of complex karyotype among patients with PEL (96% vs 61%; $P < .001$). Among patients with PEL, median number of cytogenetic abnormalities was 20 (range, 9-47), and median number of cytogenetic clones was 2 (range, 1-6). The most frequently involved chromosomes were chr5 (21 [81%] of 26), chr7 (15 [58%] of 26), and chr17 (14 [54%] of 26). Monosomal karyotype was observed in 16 patients (62%).

Targeted sequencing was performed in 12 patients (44%) with PEL. The most frequently mutated gene was *TP53*, detected in 11 (92%) of 12 patients, followed by *ASXL1* (*G646fs**), *PTPN11* (*G503R*) and *DNMT3A* (*L798P*), each present in 1 patient (8%). Sixteen *TP53* mutations were identified among patients with *TP53*-mutated PEL (Figure 1A). The median variant allele frequency of *TP53* mutations detected from whole bone marrow was 0.22 (range, 0.04-0.52). Variant allele frequency estimates were used to evaluate clonal and subclonal relationships within each individual sample,²⁰ with clonal heterogeneity being defined in cases with Pearson goodness-of-fit P values $< .05$. Among 7 patients evaluable for clonal heterogeneity testing, 3 (43%) were clonally heterogeneous and carried at least 1 subclone (supplemental Figure 1). Allelic frequencies of *TP53* mutations suggested that a founder *TP53* mutation was always present. Five patients carried 2 different *TP53* mutations, with the minor *TP53* mutation appearing to be clonally related in 3 and subclonally related in 2 patients (Figure 1B). Among 11 patients (41%) with both sequencing and cytogenetic data, 4 (36%) possessed a co-occurring *TP53* mutation and chr17 abnormality (supplemental Figure 2). More than 1 *TP53* anomaly, either resulting from mutation or loss of chr17, was detected in 8 (73%) of 11 of these patients. Targeted sequencing was available in 17 patients (10.5%) with AEL. Mutations in *TP53* were observed in 7 patients (41%), 3 of whom had 2 different *TP53* mutations (supplemental Table 4). Among the patients with AEL for whom sequencing was available, 10 (59%) had complex karyotype, but only 1 had a chr17 abnormality, and this patient did not have any *TP53* mutation detected.