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Incidence of QT interval prolongation during arsenic trioxide-based therapy in a sample of Iraqi adult patients with acute promyelocytic leukemia (a single-center experience)

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Abstract:

BACKGROUND: Arsenic trioxide (ATO) regimen is now the standard of care for acute promyelocytic leukemia (APL). The complete remission and possible cure are reported to be 50%–80% of APL patients. Prolongation of the QT interval has been consistently observed in clinical trials with ATO, which is known to have a direct effect on cardiac repolarization with the recommendations for management include electrocardiogram (ECG) monitoring, discontinuation of drugs that prolong the QT interval, and careful repletion of serum potassium and magnesium.

OBJECTIVES: To study the incidence and clinical consequences of QT prolongation in a sample of Iraqi APL patients treated with ATO.

PATIENTS AND METHODS: A prospective, cross-sectional study was conducted on 24 adult patients with newly diagnosed APL at Baghdad Teaching Hospital. ECG was performed at baseline and twice weekly till the end of induction treatment course. Corrected QT interval was calculated based on Bazett and Fridericia formulas (QTc interval of more than 500 ms is considered dangerous): Serum potassium, calcium, and magnesium levels were also measured simultaneously.

RESULTS: The mean QT at baseline was 424 ± 18 ms and 402 ± 15 ms by Bazett and Fridericia, respectively, and at the end of induction, the mean QT was 436 ± 20 ms and 418 ± 20 ms by Bazett and Fridericia, respectively. The rate of developing prolonged QT was 62.5% by Bazet, in which 15 patients developed prolonged QT (at any time point). The comparison between prolonged and dangerous QT groups by Bazet showed significant difference, in which QT-related complications were associated with dangerous QT (>500 ms) prolongation significantly, while Fridrica method did not label these patients as having dangerous QT prolongation. The change in QT started as early as 1 week after treatment, the comparison between baseline QT and QT at week 1 showed that there was significant increase in QT. The electrolytes analysis and comparison with baseline results for potassium, magnesium, and calcium showed that there were no significant differences over time for tested electrolytes.

CONCLUSION: Bazett formula is useful to monitor Iraqi patients with APL who are treated with ATO for the detection of dangerous prolongation of QT.

Keywords:

Acute promyelocytic leukemia, arsenic trioxide, prolonged QT

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Introduction

Acute promyelocytic leukemia (APL) is characterized by the accumulation of

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immature promyelocytes in the blood marrow and it is associated with an aggressive behavior.[1,2]

APL comprises 5%–15% of acute myeloid leukemia (AML) case globally.[3] In Iraq, a recent study showed that the APL contributes to 13.9% of acute myloid leukemia in Iraq.[4] While some other reports from Kurdistan region showed higher percentage of APL, in which, in Erbil, the APL was representing 13% of total AML cases diagnosed from 2007 to 2016.[5] In Sulaimaniyah, the APL prevalence was higher, it was representing 25.5% of total AML cases diagnosed from 2013 to 2018.[6]

After the initial therapeutic success reported using an anthracycline (daunorubicin), the management and outcome of APL have been revolutionized by the introduction of all-trans retinoic acid (ATRA; tretinoin) and arsenic trioxide (ATO). The complete remission and possible cure are reported to be 50%–80% of APL patients. Prolongation of the QT interval has been consistently observed in clinical trials with ATO, which is known to have a direct effect on cardiac repolarization with recommendations for the management include electrocardiogram (ECG) monitoring, discontinuation of drugs that prolong the QT interval, and careful repletion of serum potassium and magnesium.[7]

There is a black box warning about potentially fatal torsades de pointes associated with ATO in which polymorphic type of ventricular arrhythmia may be manifested with ATO management for APL patients.[8] The most frequently used method for calculating the QTc is the Bazett formula, $QTc = QT/\sqrt{RR}$. Bazett published the first version of this formula in 1920 using ECGs from 39 young subjects and was subsequently updated by Taran and Szilagyi in 1947. The Fridericia formula ($QTc = QT/RR^{1/3}$) was also developed in 1920.[2]

Hence, the aim of this study was to study the incidence and clinical consequences of QT prolongation in a sample of Iraqi APL patients treated with ATO-based protocol.

Patients and Methods

A prospective, cross-sectional study conducted on 24 adult patients as newly diagnosed adult APL at Baghdad Teaching Hospital whose the diagnosis was confirmed by flow cytometry and polymerase chain reaction (PCR) or fluorescence *in situ* hybridization (FISH) study. The patients have been admitted to Baghdad Teaching Hospital, Hematology Department in Medical City Complex. The study population consisted of 24 patients with newly diagnosed APL.

Inclusion criteria

1. Confirmed diagnosis of APL patients (flow cytometry and PCR or FISH study)
2. Age 14 years old and above
3. Serum creatinine and bilirubin levels ≤2.5 × the upper limit of normal
4. Eastern Cooperative Oncology Group performance status ≤2
5. Negative pregnancy test result in women of childbearing age.

Exclusion criteria

1. Patient whose ECG show tracings of poor quality (baseline artifact, markedly flattened T-waves, and marked tachycardia with P on T)
2. Patients with confounding ECG abnormalities (nonsinus rhythm, bundle branch block, and frequent ectopic complexes)
3. Uncontrolled heart failure or baseline QTc prolongation.

Calculating the QTc interval

The QTc interval was calculated using Bazett formula and Fridericia formula.

The following formulas were used:[2]

- Bazett: $QTcB = QT/RR^{1/2}$
- Fridericia: $QTcFri = QT/RR^{1/3}$

We used the WHO 2016 Guidelines for QTc interpretation, considering a QTc value of > 450 ms among males, or 470 ms among females, or an increase of 60 ms from baseline to be prolonged and requires that electrolyte testing and more frequent ECG monitoring are performed. A QTc interval of more than 500 ms is considered dangerous.[9]

Ethical consideration

The study was approved by scientific committee of pathology department in Baghdad medical college. All

Table 1: Demographic characteristics of the patients

Variable	*n* (%)
Age, mean±SD (years)	36.08±15.4
Blood urea (mg/dL)	38.4±17.5
Serum creatinine (mg/dL)	0.91±0.23
Gender	
Male	14 (58.3)
Female	10 (41.7)
Co-morbidities	
DM	3 (12.5)
Hypertension	3 (12.5)
Thyrotoxicosis	1 (4.2)
Echo examination	
Hypertension LVH	2 (8.3)
Normal	22 (91.7)
ECOG	
0	22 (91.7)
2	2 (8.3)

SD=Standard deviation, DM=Diabetes mellitus, LVH=Left ventricular hypertrophy, ECOG=Eastern Cooperative Oncology Group

patients were interviewed and explain to them nature of study and they gave their informed consent prior to study.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software version 23 (IBM SPSS, Inc., Chicago, USA) had been used for the data entry and analysis. In the descriptive statistics for sociodemographic characteristics, the means, standard deviations, minimum, and maximum values were used for the continuous data. Numbers and percentage values were used for the countable data. In analyzing the differences between the groups, Pearson correlation has been used to find the correlation between two continuous variables. Paired sample *t*-test has been used to compare same population variables over time. The linear regression has been used to assess the factors associated with QT interval. $P < 0.05$ was used as the threshold for statistical significance.

Results

There were 24 patients who completed treatment and their response had been evaluated. The mean age of patients was 36.08 ± 15.4 years (range 15–65). The mean baseline urea was 38.4 ± 17.5 mg/dL and creatinine was 0.91 ± 0.23 mg/dL. Females represented majority of cases (58.3%) and males represented (41.7%) of patients. Regarding the comorbidities, there were 3 (12.5%) patients with hypertension, 3 (12.5%) had diabetes, and one patient had a history of thyrotoxicosis [Table 1].

QT calculation

The mean QT at baseline was 424 ± 18 ms and 402 ± 15 ms by Bazett and Fridericia formulas, respectively, and at the week 5, the mean QT was 436 ± 20 ms and 418 ± 20 ms by Bazett and Fridericia formulas, respectively [Table 2].

The rate of developing prolonged QT was 62.5%, as 15 patients developed prolonged by Bazett and 29.1% pateints developed prolonged QT by Fridericia (at any time point) [Figure 1].

Risk stratification

The risk stratification of the patients based on Bazett and Fridericia formulas is given in Table 3.

Prolonged QT group by Bazett (*n* = 15 patients)

The mean age across patients with prolonged QT was 38.9 ± 14.2 years (range 18–65 years). Majority of

Table 2: Mean QT interval based on Bazett and Fridericia

Time	Mean±SD (ms)	
	Bazett formula	Fridericia formula
Baseline	424±18	402±15
Week 1	445±21	418±16
Week 2	454±30	435±18
Week 3	462±25	430±19
Week 4	448±23	423±21
Week 5	436±20	418±20

SD=Standard deviation

Table 3: The risk stratification over time, based on Bazett and Fridericia

	Normal/ borderline, *n* (%)	Prolonged, *n* (%)	Dangerous, *n* (%)
Bazett			
Baseline	24 (100)	0	0
Week 1	18 (75)	6 (25)	0
Week 2	17 (70.8)	4 (16.7)	3 (12.5)
Week 3	13 (54.1)	10 (41.7)	1 (4.2)
Week 4	17 (70.8)	6 (25)	1 (4.2)
Fridericia			
Baseline	24 (100)	0	0
Week 1	23 (95.8)	1 (4.2)	0
Week 2	19 (79.2)	5 (20.8)	0
Week 3	21 (87.5)	3 (12.5)	0
Week 4	22 (91.6)	2 (8.3)	0

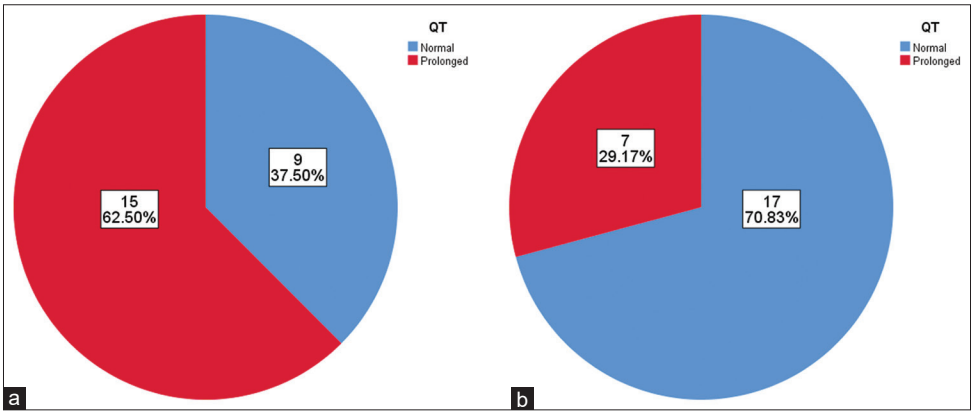

Figure 1: Frequency of patients who develop prolonged QT at any time point. (a): By Bazett. (b): By Fridericia

cases with prolonged QT were males (73.3%). There were 3 (20%) patients with prolonged QT who had comorbidities (two patients had diabetes mellitus and hypertension, one patient with thyrotoxicosis) [Table 4].

The change in QT by Bazett and Fridericia over time among prolonged versus dangerous QT group only showed increased in mean of QT starting by week one till the 4th week when the QT start to decline. K and Mg showed associated decrease in its mean starting by week 1 to 4th week when both started to increase, while serum calcium did not show any change over time. No significant difference was seen between both prolonged and dangerous QT groups for electrolytes [Figure 2].

Table 4: Characteristics of prolonged QT group (*n*=15) (by Bazett formula)

Variables	Count
Age, mean±SD (years)	38.9±14.2
Gender, *n* (%)	
Male	11 (73.3)
Female	4 (26.7)
Comorbidities, *n* (%)	
Yes	3 (20)
No	12 (80)
Urea, mean±SD (mg/dL)	38.8±16.4
Creatinine and mean±SD (mg/dL)	0.9±0.18
Prolonged QT-related complications (ventricular and superventricular tachycardia)	
Yes	2 (13.3)
No	13 (86.7)
Medication that cause prolonged QT	
Yes	8 (53.3)
No	7 (46.7)
Dangerous QT by Bazett	
Yes	4 (26.7)
No	11 (73.3)

SD=Standard deviation

Table 5: Association of prolonged QT and patients characteristics (*n*=15)

	Prolonged (*n*=11)		Dangerous (*n*=4)		*P**
	Count	N %	Count	N %	
Sex					
Female	3	27.3	1	25.0	0.93
Male	8	72.7	3	75.0	
Comorbidities					
Yes	2	18.2	1	0.0	0.17
No	9	81.8	3	100	
QT-related complication					
No	11	100	2	50.0	0.01
Yes	0	0.0	2	50.0	
Medication causes QT**					
No	4	36.4	3	75.0	0.18
Yes	7	63.6	1	25.0	

*Fisher's exact test, **Medication causes QT were, Ondansteron, metchlorpromide, levofluxacin, moxifluxacin, ciprofluxacin, loratidin, flucanazole

The comparison between prolonged and dangerous QT groups by Bazett showed significant difference, in which QT-related complications were associated with dangerous QT prolongation significantly ($P = 0.01$) [Table 5].

The change in QT started as early as week 1 after treatment, the comparison between baseline QT and QT at week 1 showed that there was significant increase in QT and the mean change from baseline was 20 ms (based on Bazett) and 17 ms (based on Fridericia) ($P < 0.05$). The increase in QT continued to week 2 and the mean change was significant between week 1 and 2 based on Fridericia only ($P = 0.025$). From week 3 and onward, the change directed toward baseline QT and the comparison between baseline QT and week 5 showed no significant difference ($P > 0.05$) [Tables 6 and 7].

The electrolytes analysis and comparison with baseline results for K^+, Mg^+, and Ca^{2+} showed that there were no significant differences in change over time for tested electrolytes ($P > 0.05$).

Discussion

As per the latest recommendation of expert panel of the European leukemia net for the management of APL, they

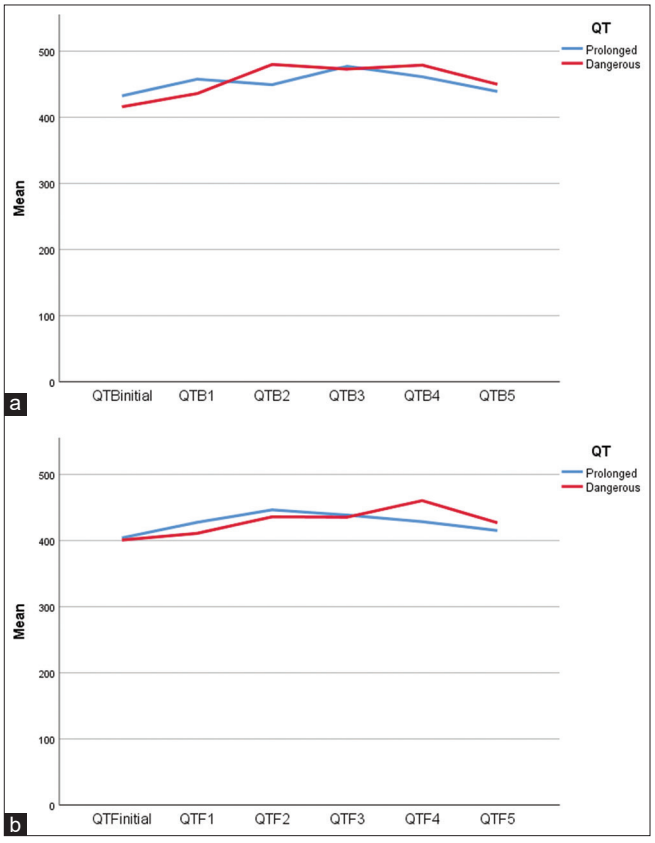

Figure 2: (a) Mean change in QT (ms) by Bazzett across prolonged and dangerous group s ($P > 0.05$ for any point). (b) Mean change in QT (ms) by Fridericia across prolonged and dangerous ($P > 0.05$ for any point) groups

Table 6: Comparison between different time points for QT interval based on Bazett

	Z-test	*P**
QT1–QT baseline	−3.2	0.001
QT2–QT1	−1.6	0.09
QT3–QT2	−1.3	0.17
QT4–QT3	−2.5	0.01
QT5–QT4	−3.2	0.0001
QT5–QT baseline	−1.3	0.18

*Wilcoxon singed-ranks test

Table 7: Comparison between different time points for QT interval based on Fridericia

	Z-test	*P**
QT1–QT baseline	−3.1	0.001
QT2–QT1	−4.1	0.001
QT3–QT2	−0.88	0.37
QT4–QT3	−1.79	0.073
QT5–QT4	−1.78	0.074
QT5–QT baseline	−2.1	0.048

*Wilcoxon singed-ranks test

add new recommendation that; treatment with ATO requires monitoring of the QT/QTc interval at least twice weekly, in which, routine ECG surveillance of QT interval prolongation, alternative rate adjustment formulas other than the classical Bazett correction (e.g., Fridericia) should be used. Furthermore, they recommended if the QT interval is prolonged longer than 500 ms, ATO should be withheld, the electrolytes repleted (potassium and magnesium), and other medications that may cause prolonged QTc interval sought and possibly discontinued. Then, once the QT/QTc returns to ~460 ms and the electrolytes are replete, ATO may be resumed.[10]

Based on that, we calculated the QT interval by Bazett and Fridericia equation over 5 weeks of follow-up during induction by ATRA and ATO. The mean QT at baseline was 424 ± 18 ms and 402 ± 15 ms. by Bazett and Fridericia, respectively. The peak mean was observed from 2 to 3 weeks after initiation of ATO and ATRA.

The rate of developing prolonged QT was 62.5%, in which 15 patients developed prolonged QT (at any time point by Bazett), while only seven (29.1%) patients developed prolonged QT (at any time point by Fridericia). This rate was higher in Lo-Coco *et al*. study that showed that 16% of their patients developed prolonged QT.[11] Importantly, Lo-Coco *et al*. used Framingham formula for QT interval calculation. On the other hand, another study by Kayser *et al*. showed that only 1.6% of their patients developed prolonged QT.[12]

Furthermore, in another study Sun *et al*. showed that, 7.5% of their APL (regardless severity) patients developed dangerous QT prolongation.[13] In Sun *et al*. study, four patients had supraventricular tachycardia and three patients had QTc 500 ms or more, and thus, had to discontinue ATO therapy. The arrhythmias in Sun *et al*. study occurred during ATO therapy from days 22 to 29, QTc prolongation and supraventricular tachycardia were the frequent adverse effects of ATO. When QTc increases to 500 ms or more and supraventricular tachycardia happened, considering of drug safety, the patients had to discontinue ATO therapy until QTc or cardiac function was back to normal.[14]

Furthermore, 16 of 40 patients (40%) in the United States Multicenter Study of ATO had prolonged QTc. One patient in this group, with hypokalemia and on amphotericin B, developed an asymptomatic 7-beat run of ventricular tachycardia with spontaneous reversal.[15]

Autopsy studies in a patient who developed complete heart block while on ATO showed high arsenic levels in the cardiac tissue.[16]

Roboz *et al*. carried out a study in patients with non-APL AML and myelodysplastic syndrome treated with ATO combined with low-dose cytarabine, the main conclusions drawn based on extensive ECG data can be extrapolated to the use of ATO in APL. In this study, based on 113 patients treated with ATO, 90% had QTc prolongation >470 ms with 65% above 500 ms when rate correction was performed with the standard Bazett formula, yet none developed severe or clinically relevant arrhythmias. In contrast, the use of alternative rate-correction formulas (Fridericia, Hodges, or Sagie/Framingham) indicated that 24%–32% of patients had rate-corrected QT intervals above 500 ms. Thus, use of these formulas will result in a reduction of unnecessary interruptions of ATO therapy.[17]

Furthermore, a study of effect of ATO on QT interval in patients with advanced solid malignancies by Barbey *et al*. showed that prolonged QT intervals developed in 38 patients (26 patients had intervals ≥ 500 ms). Compared with baseline, the heart rate (HR)-corrected (QTc) interval was prolonged by 30–60 ms in 36.6% of treatment courses, and by more than 60 ms in 35.4% of patients.[18] This indicates the generalized effect of ATO across all malignancies. Furthermore, it is important to mention that cancer patients are more susceptible to longer QTc interval as demonstrated by Kim *et al*. study.[19]

In this study, the association between prolonged and dangerous QT groups showed significant difference with prolong QT-related complications, in which QT-related complication was associated with dangerous QT prolongation significantly. The complication was ventricular and supraventricular tachycardia in two patients, both diagnosed as a case of low-risk AML (M3) and received ATO in dose of 0.15 mg/kg with normal

initial ECHO, renal and liver function tests, electrolytes, and QT interval.

The first patient was a 33-year-old male with negative past medical history and at day 15 of ATO and ATRA treatment and after about 6 h of administration developed a short term of palpitation and ECG at that time show sinus rhythm with prolonged QT interval (503 ms) by Bazett and (462 ms) by Frederica after about ½ h patient developed ventricular tachycardia and responded well to 150 joules cardioversion and electrolytes replacement which was low at that time (S.K + 2.2 mmoL/L, S.Mg + 2 1.3 mg/dL) and ATO was stopped for 2 days.

The second patient 53-year-old female with a history of thyrotoxicosis treated before 3 years and was in remission with normal thyroid function test at presentation, at day 13 of ATO treatment patient developed an attack of palpitation and chest tightness ECG was of supraventricular tachycardia that necessitated admission to CCU and after resolution of the first attack she developed another attack after about 1 h from the first one in which both responded to adenosine injection with ECG between the 2 event show QTc (510,480 ms.) by Bazet and Federica, respectively, while serum electrolytes an thyroid function test were normal at that time the patient was on (ondansetron and azithromycin) which both listed to cause prolonged QT interval, ATO and other agent that cause prolonged QT were stopped for 2 days then reassumed after QTc was 460 ms with no further complication.

Based on KNCV 2018 recommendation, patients who reached an absolute QTc interval value longer than 500 ms or those who developed syncope, tachycardia, or arrhythmia should be hospitalized for ECG and electrolyte monitoring, ATO should be temporarily withheld, together with other medications that may prolong the QTc interval, whenever possible. ATO may be resumed at 50% of dose and later increased to full dose when the QTc returns to ~460 ms, provided that electrolytes are repleted.[3]

Rather similar findings were found by Unnikrishnan *et al*., of eight patients included in their cohort, three patients developed ventricular tachycardia (torsade de pointes).[20] Furthermore, sinus tachycardia, ventricular premature contractions, nonsustained ventricular, and supraventricular tachycardia were noted during continuous cardiac monitoring during ATO treatment in Unnikrishnan *et al*. study.[20]

Ohnishi *et al*. showed that 5 APL patients on ATO developed prolonged QT and one of them developed ventricular tachycardia.[21]

The change in QT started as early as week one after treatment, the comparison between baseline QT and QT at week 1 showed that there was significant increase in QT and the mean change from baseline was 20 ms (based on Bazett) and 17 ms (based on Fridericia) ($P < 0.05$). The increase in QT continued to week 2 and the mean change was significant between week 1 and 2 based on Fridericia only ($P = 0.025$). From week 3 and onward, the change directed toward baseline QT and the comparison between baseline QT and week 5 showed no significant difference ($P > 0.05$). This was in line with Sun *et al*. study in which they reported a QT changes started at day 8 after treatment.[13]

The electrolytes analysis and comparison with baseline results for K, Mg, and Ca showed that there were no significant differences in change over time for tested electrolytes in relation to QT changes. On the other hand, few other studies showed that hypokalemia is associated with development of prolonged QT.[18,22]

It is clear that the magnitude of drug-related QT prolongation varies with the method of measurement and with the mathematics of rate correction of the measured QT.[23,24] The Bazett correction, widely used over the past 90 years, is well-known to overcorrect the QTc when HRs are above 80 beats per minute. Thus, the Bazett formula produces higher corrected QT values than would occur with more rate-independent means of adjustment.[25] It is evident from our data that more patients have been truly identified to have dangerous prolonged QT(<500 ms) in the Bazett formula while still none dangerous with Fridericia QT measurement and 2 of them developed life threatening conditions. For these reasons, we believe that adjustment of the uncorrected QT interval by using one of the alternate formulas, such as Fridericia, although is appropriate to screen for potentially important QT intervals that might be missed at faster HRs with uncorrected QT, while among Iraqi patients, the Bazett formula identified the patients who would likely develop symptomatic tachycardia.

Conclusion

Bazett formula is useful to monitor Iraqi patients with APL treated with ATO-based regimen to detect the dangerous prolongation of QT.

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Conflicts of interest
There are no conflicts of interest.

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