QT prolongation due to targeted anticancer therapy

Lucia Setteyova, MD[1,3], Ljuba Bacharova, MD, DSc, MBA[1,2], Prof. Beata Mladosievicova, MD, PhD[1]

[1] *Institute of Pathological Physiology, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic*

[2] *International Laser Centre, Department of Biophotonics, Bratislava, Slovak Republic*

[3] *Clinic of Hematology and Transfusiology, Faculty of Medicine, Comenius University and Slovak Medical University, Bratislava, Slovak Republic*

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ABSTRACT

A growing number of targeted anticancer agents has shown the unexpected ability to induce QT interval prolongation. In addition, standard chemotherapeutics and a variety of conditions such as electrolyte abnormalities, endocrine disorders, cardiac diseases, nutritional disturbances and other factors may be associated with long QT syndrome in cancer patients. Prolongation of the QT interval can lead to life-threatening ventricular arrhythmias, including 'torsade de pointes' (TdP). The association between long QT interval and ventricular arrhythmias remains the subject of many controversies.

The QT interval represents the time interval of both ventricular depolarization and repolarization. Not only abnormalities of ion channels, but also changes in the myocardial microarchitecture and other factors and disorders frequently seen in cancer patients may participate in its prolongation and potential risk of ventricular arrhythmias.

The aim of this review was to summarize current knowledge about QT prolongation in cancer patients with the special focus on targeted therapy.

KEY WORDS: QT prolongation, targeted therapy, torsade de pointes, cancer patients

Correspondence:
Prof. Beata Mladosievicova, MD, PhD
Institute of Pathological Physiology, Faculty of Medicine,
Comenius University, Bratislava
811 08 Bratislava, Sasinkova 4, Slovak Republic
e-mail: beata.mladosievicova@fmed.uniba.sk
tel.: (+421) 259-357-604; fax: (+421) 259-357-601

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INTRODUCTION

More than thirty antineoplastic drugs have been shown to cause prolongation of the QT interval and increased risk of life-threatening ventricular arrhythmias, specifically TdP in cancer patients (tab. 1). In the era of targeted therapy this problem becomes increasingly important.

Additionally to mechanisms leading to the long QT syndrome in cancer patients, several anticancer drugs without QT prolongation effects may increase the proarrhythmic potential indirectly by causing myocardial ischemia, edema, hemorrhage, myocarditis, congestive heart failure, left ventricular hypertrophy, bradyarrhythmia, complete atrioventricular block or electrolyte abnormalities [1].

Also, numerous drugs used in the supportive care of cancer patients such as antimicrobials, antidepressants, antiemetics and others are associated with QT prolongation. A number of them can affect ion channels.

Potentially life-threatening ventricular arrhythmias can occur especially when multiple hits contribute to the proarrhythmic state. The loss of myocardial cells, fibrosis, edema, hemorrhage, ischemia and reduced intercellular coupling caused by antineoplastic agents in the presence of abnormalities of the ion channels can potentiate the risk of arrhythmias.

TABLE 1.
Antineoplastic drugs with known and potential QT prolongation [31, 57].

Anthracyclines	Tyrosine kinase inhibitors
Doxorubicin Daunorubicin Epirubicin Idarubicin	Dasatinib Nilotinib Lapatinib Pazopanib Sunitinib Sorafenib Vandetanib Bosutinib Ceritinib Crizotinib
Alkylating agents	
Cyclophosphamide Ifosfamide	
Antimetabolites	
5-Fluorouracil Methotrexate	
Immunosuppressants	
Tacrolimus	
Microtubule inhibitors	**FLT3 inhibitors**
Eribulin mesylate	Quizartinib
Platinum-based agents	**BRAF inhibitors**
Oxaliplatin Cisplatin	Dabrafenib Vemurafenib
Intercalating agents	**Proteasome inhibitors**
Amsacrine	Bortezomib
GnRH agonists/antagonists	**Histone deacetylase inhibitors**
Degarelix Leuprolide	Vorinostat Panobinostat Romidepsin
SERMs	**Other antineoplastics**
Tamoxifen Toremifene	Arsenic trioxide

GnRH – gonadotropin releasing hormone, SERMs – selective estrogen receptor modulators.

AIM

The aim of this review was to summarize current knowledge about long QT syndrome in cancer patients with the special focus on targeted therapy as well as some aspects that were not previously covered. We also aimed to assess the evidence regarding severity of QT prolongation in cancer patients.

METHODOLOGY

A systematic literature search was performed for the period of January 1975 and December 2015, using databases such as Pubmed/MEDLINE and Cochrane. Examples of keywords used included torsade de pointes, sudden cardiac death, ECG monitoring, cancer patients, QT prolongation, targeted therapy, tyrosine kinase inhibitors, monoclonal antibodies.

Two reviewers independently assessed the eligibility of the articles and abstracts identified by the search. We excluded publications where the association between long QT interval and TdP/VT was not clearly defined.

TARGETED THERAPY ASSOCIATED WITH LONG QT SYNDROME

Tyrosine kinase inhibitors

Targeted drugs were initially expected to be safer than traditional chemotherapies, but unfortunately, cardiotoxicity issues have emerged [2]. The cardiotoxicity of tyrosine kinase inhibitors (TKIs) can be missed by the standard preclinical assessment methods such as hERG testing in *in vitro* studies or testing in animal studies [3].

However, QT prolongation has been observed with several TKIs. Sunitinib, vandetanib and pazopanib have been associated with the occurrence of TdP, nilotinib and vandetanib with sudden cardiac death [4–7]. Black box warning regarding long QT syndrome, TdP and sudden death has been approved for nilotinib and vandetanib [4, 8].

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In a recent meta-analysis with 6548 patients, Ghatalia et al. reported an 8.66-fold increase in the risk of all grades of QT prolongation and a 2.69-fold increase in the risk of high-grade QT prolongation in patients exposed to TKIs [9]. Higher risk of QT prolongation was associated especially with vandetanib and sunitinib. The risk of prolonged QT interval with TKIs in this study was greater at higher doses which becomes increasingly important considering possible concomitant medication with the other drugs that have their own QT prolongation potential [9]. Based on the data from some authors, QT prolongation associated with vandetanib varies from 0.4% to 18% and from 3.7% to 8% for grade 3–4 QT prolongation [10, 11]. The mean QTF change from baseline for the standard dose was 35 ms and remained above 30 ms during the trial (up to 2 years) [8, 11]. According to the FDA database TdP has been observed in 0.1% of patients treated with vandetanib [12].

The QT prolongation effect was originally assumed to be due to the inhibition of I_{Kr} current. However, not all TKIs prolong the QT interval and not all TKIs block I_{Kr} at therapeutic concentrations [13]. Long QT syndrome induced by TKIs is caused by the inhibition of the phosphatidylinositol 3-kinase (PI3K) signalling pathway which is known to affect multiple ion channels [14]. As a result, abnormalities of several ion currents may be involved (tab. 2) [15]. Interestingly, when compared with other TKIs, nilotinib causes weaker inhibition of I_{CaL} and it blocks also I_{Ks} current which could partially explain why is nilotinib associated with higher risk of ventricular arrhythmias.

Decrease in myocytes viability and their loss is also induced by some of TKIs [16]. In the study by Freebern et al., dasatinib, which is known to cause only mild QT prolongation, did not decrease cardiomyocytes viability neither resulted in their loss [17]. On the other hand, nilotinib associated with the risk of sudden death, significantly affected these characteristics [15, 17]. Sunitinib also induced mitochondrial injury and the loss of cardiomyocytes in mice and in cultured rat myocardial cells [18]. These experimental results demonstrate that some of the TKIs directly induce loss of cardiomyocytes. In a preclinical model, lapatinib caused a significant increase in cardiac fibrosis in contrast to control mice [19].

Ponatinib, a novel multi-targeted TKI, has been associated with cardiovascular toxicities such as myocardial infarction, severe congestive heart failure and cardiac arrhythmias [3]. During phase 1 trial of ponatinib, treatment related QT prolongation was observed in 7,7% (n = 3) of patients, mostly in the presence of concomitant medication [20].

In study by Talbert et al. ponatinib potently inhibited pro-survival signalling pathways, caused structural cardiotoxicity including cell death, an increase in troponin and induced disruption of cardiac cell beating. In addition, prolonged therapy with ponatinib in lower doses also caused significant structural damage [3].

TABLE 2.
Direct effects of anticancer drugs on Ion channels.

Drug class	Ion channels				
	Depolarization			Repolarization	
	I_{Na}	I_{NaL}	I_{CaL}	I_{Kr}	I_{Ks}
Anthracyclines					
Doxorubicin			↑ [58]	- [59]	↓ [59]
Daunorubicin					
Epirubicin					
Idarubicin					
Platinum-based agents					
Oxaliplatin	↑ [60]				
Intercalating agents					
Amsacrine				↓ [61]	
SERMs					
Tamoxifen	↓ [62]		↓ [63]	↓ [63]	
Toremifene				↓ [64]	
TKIs					
Dasatinib				↓ [17]	
Crizotinib	↓ [15]	- [15]	↓ [15]	↓ [15]	
Nilotinib	↓ [14]	↑ [14]	↓ [14]	↓ [14]	↓ [14]
Sunitinib	↓ [15]	- [15]	↓ [15]	↓ [15]	
Erlotinib	↓ [15]	- [15]	↓ [15]	↓ [15]	
Lapatinib	- [65]		- [65]	↓ [65]	↓ [65]
HDAC inhibitors					
Panobinostat				↓ [41]	
Other antineoplastics					
ATO			↑ [66]	↓ [67]	↓ [67]

INa – peak sodium current, INaL – late sodium current, ICaL – L-type calcium current, IKr – rapid component of the delayed rectifier potassium current, IKs – slow component of the delayed rectifier potassium current, SERMs – selective estrogen receptor modulators, TKIs – tyrosine kinase inhibitors, HDAC – histone deacetylase inhibitors, ATO – arsenic trioxide, ↑ – activation, ↓ – inhibition, - – no effect.

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BRAF INHIBITORS

Small-molecule BRAF inhibitors allowed great advances in therapy of various malignancies. The reported rate of QT prolongation in patients treated with vemurafenib varies from 7% to 11%, 1–2% of patients in these studies experienced QT prolongation of more than 500 ms [21, 22]. So far, no case of TdP induced by BRAF inhibitors has been documented.

Proposed mechanisms of cardiotoxicity include an increase in cAMP activity and phosphorylation of hERG channels and resulting decrease in their function. The other hypothesized mechanism is down-regulation of hERG channel protein quality and quantity [23].

FLT3 Inhibitors

Quizartinib is a novel potent second-generation small molecule TKI designed as a specific inhibitor of the fms-like tyrosine kinase 3 (FLT3).

In a phase I trial out of 76 patients treated for relapsed or refractory acute myeloid leukemia (AML) 12% patients developed prolonged QT and 5% of patients were diagnosed with grade 3 (> 500 ms) QT prolongation which led to the reduction of dose of quizartinib from 200 mg per day to lower doses in subsequent phase II trials [24]. The phase II study enrolled 76 patients with relapsed or refractory (AML) randomized to use either 30 mg or 60 mg of quizartinib per day [25]. The occurrence of grade 2 QT prolongation was 11% in the 30 mg arm, 17% in the 60 mg arm and grade 3 QT prolongation was 3% in both arms. There was no grade 4 QT prolongation. The mean maximum QT prolongation was 31.5 ms vs 39.7 ms in 30 mg and 60 mg arms respectively [25]. Prevalence of QT prolongation from two cohorts which included 134 and 137 patients was 25–26% [26, 27]. The mechanism of QT prolongation is unknown.

Proteasome inhibitors

Isolated cases of QT prolongation in clinical studies have been reported, however, several trials tested bortezomib in combination with histone deacetylase inhibitors which also possess QT prolongation potential [28, 29]. Therefore, causality needs further investigation.

In clinical trial with 11 patients treated for relapsed or refractory acute myeloid leukemia two patients developed long QT syndrome, one followed by TdP [30]. As a result, the Arizona Center for Education and Research on Therapeutics (AzCERT) listed bortezomib as drug with possible TdP risk [31].

Proteasome inhibition may induce loss of cardiomyocytes via endoplasmic reticulum stress and ischemic complications caused by the destabilization of atherosclerotic plaque [32, 33]. Direct effect on specific ion channels is unknown.

Histone deacetylase inhibitors

QT prolongation resulting into TdP and several cases of unexpected death has been reported with romidepsin [34].

In a phase II trial with romidepsin, the mean QT prolongation was 14.4 ms when compared with the baseline values [35].

Panobinostat has obtained black box warning regarding severe arrhythmias, ECG changes and severe and fatal cardiac ischemic events [36]. According to the package insert, QT prolongation with values between 451 and 480 ms was detected in 10.8% of patients, values between 481 to 500 in 1.3% of patients [36]. The overall incidence of QT prolongation > 500 ms is approximately 1% overall and 5% and more at higher doses [36]. Vorinostat was reported to cause long QT syndrome and TdP, interestingly, in preclinical study it showed only little effect on hERG channels and in QT phase I study single supratherapeutic dose of vorinostat did not prolong QT interval [37–39]. The incidence of QT prolongation associated with vorinostat is 3.5–6% [40].

In a phase I study of vorinostat in combination with bortezomib, among 23 patients 6 patients developed QT prolongation, however, only one patient had QT greater than 500 ms [28].

Since some of HDAC inhibitors were documented to inhibit hERG channels, hERG inhibition has been proposed to be a class effect [41]. In preclinical studies, romidepsin has been reported to produce direct myocardial injury with cardiac enzyme elevation, myocardial inflammation and epicardial or endocardial hemorrhage [42].

RECOMMENDATIONS FOR QT EVALUATION DURING TARGETED THERAPY

Despite the unknown prevalence of drug-induced TdP in cancer patients, the potential risk can be reduced by carefully obtaining the patient's medical history or by treatment of disorders, such as bradycardia, thyroid dysfunction or cardiovascular disease and electrolyte dysbalancies [43].

According to expert-opinion Clinical Practice Guidelines of European Society of Medical Oncology published in 2012 in An-

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nals of Oncology, a standard 12-lead ECG should be recorded before anticancer treatment with potential cardiotoxicity and the QT time should be corrected for heart rate (QT) with Bazett's formula (QT = QT/√RR) [43]. Recommendations for QT evaluation during and after potential cardiotoxic anticancer therapy are not included in this document.

Recently, detailed clinical recommendations for monitoring of patients receiving targeted anticancer drugs, such as vorinostat, romidepsin, dasatinib, nilotinib sunitinib, pazopanib, vandetanib and arsenic trioxide to prevent QT interval prolongation and TdPs were published by Yeh et al. [44]. According to these authors risk factors leading to QT prolongation should be carefully identified and eliminated when possible [44].

DISCUSSION

The association between long QT interval and ventricular arrhythmias remains the subject of many controversies. QT prolongation induced by anticancer agents is not rare. In the study by Cipolla out of 700 patients who had normal QT in the baseline 15–20% patients developed prolonged QT during chemotherapy [45]. However, even increase in QT interval more than 60 ms over baseline was not associated with the occurrence of ventricular arrhythmias [45]. A high percentage of patients (35%) with a baseline long QT normalized QT interval during chemotherapy. This author concluded that QT prolongation is more probably the manifestation of cardiological comorbidity than the effect of chemotherapy.

It seems that the occurrence of TdP associated with the prolongation of the QT interval is presumably low. The estimated incidence of torsade de pointes (TdP) caused by non-antiarrhythmic drugs varies from < 1 in 10 000 to 1 in 100 000 cases [46]. Yet, some fatal cases of TdP have been associated with the presence of risk factors. In the study of Zeltser et al. from reported 249 cases with TdP induced by non-cardiac drugs all patients had at least one predisposing risk factor and 71% of these patients had two or more risk factors [47]. The most frequent risk factor for TdP in this study was female gender (71%) [47].

Moreover, there are several criteria for evaluation of the QT interval (tab. 3). An increase in QT/QTc to > 500 ms or > 60 ms over baseline value has been associated with the risk of TdP and according to the FDA International Conference on Harmonization E14 (ICH E14) guidance document it is also the threshold for potential discontinuation in QT studies [48]. Published criteria are not uniform in terms of evaluation of the QT interval on the basis of gender. European Regulatory Guidelines defined values 450–470 ms in women as borderline QT interval. However, recent statement of ICH E14 concerning clinical evaluation of QT interval prolongation proposed unified approach without the specification of QT values according to the gender by the fact that it is irrelevant to larger durations [49].

By the definition, the QT interval represents the time of depolarization and repolarization of the ventricles. Therefore, alteration in both depolarization and/or repolarization can contribute to QT prolongation.

Evidence of the effects of anticancer drugs on the ion channels, especially the hERG (human ether-à-go-go-related gene) inhibition has been published [50, 51]. Recently, it has been documented that inhibition of the hERG potassium channel prolongs equally both early and late repolarization. On the contrary, additional inhibition of the L-type calcium current (I_{CaL}) and/or late sodium current (I_{NaL}) preferentially shortens early repolarization and thus mitigates the torsadogenic risk [52]. This could contribute to the understanding of drugs that are associated with QT prolongation, but rarely lead to TdP.

However, there is a little information about the effect of anticancer drugs on QRS complex representing the ventricular depolarization. It is documented that not only the abnormalities of ion channels, but also other factors on the level of intercellular communication can create the substrate for triggering and maintaining ventricular arrhythmias. A loss of myocardial cells, edema, hemorrhage, ischemia, fibrosis and intercellular uncoupling could also be involved in arrhythmogenesis. In combination with multiple channel hit it could explain why some QT prolonging agents are associated with ventricular arrhythmias and other are devoid of arrhythmogenic effects.

Separation and distortion of cardiomyocytes caused by interstitial processes such as inflammation, fibrosis, edema or hemorrhage may lead to abnormal electrical activation (tab. 4). Cardiac fibrosis contributes to arrhythmogenesis by slowing of conduction through heterocellular gap junctions between myocytes and fibroblasts [53]. Additional mechanisms are formation of microreentrant circuits resulting from depolarization of cardiomyocytes by electrically coupled myofibroblasts and heterogenous spatial distribution of fibrous tissue [54, 55].

It is well known, that myocardial fibrosis correlates strongly with an increased incidence of arrhythmias and sudden cardiac death [55]. An increase in the extracellular volume fraction of

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myocardial fibrous tissue on the level of 3% (evaluated by cardiovascular magnetic resonance) is associated with a 50% increase in the risk of fatal cardiac events [56].

All of these factors create a potential for the heterogeneity both on a macroscopic and a microscopic level.

In addition, variety of conditions such as electrolyte abnormalities, endocrine disorders, cardiac diseases, nutritional disturbances and other factors may be associated with long QT syndrome in cancer patients (tab. 5). Coexistence of them is a common situation which makes this group particularly susceptible to QT prolongation.

TABLE 3.
Criteria for QT interval prolongation [48, 68, 69].

European Regulatory Guidelines		
	Men	Women
Normal QT	< 430 ms	< 450 ms
Borderline QT	430–450 ms	450–470 ms
Prolonged QT	> 450 ms	> 470 ms
National Cancer Institute Criteria for Prolonged QT interval		
Grade I	QT > 450–480 ms	
Grade II	QT > 481–500 ms	
Grade III	QT ≥ 501 ms on at least two separate ECGs	
Grade IV	QT ≥ 501 ms or > 60 ms change from baseline and TdP or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	
International Conference on Harmonization Guidance E14		
Absolute QT interval prolongation		Change from baseline value in QT interval
QT > 450 ms		QT increases > 30 ms
QT > 480 ms		QT increases > 60 ms
QT > 500 ms		

TABLE 4.
Pathological processes affecting myocardial interstitium.

Drug class	Inflammation	Fibrosis	Hemorrhage	Edema
Anthracyclines				
Doxorubicin	x [70]	x [71, 72]		
Daunorubicin	x [73]	x [71, 74]		
Epirubicin	x [75]	x [75]		
Idarubicin				
Alkylating agents				
Cyclophosphamide	x [76, 77]	x [76]	x [77]	x [76]
Ifosfamide	x [76]	x [76]	x [76]	
Antimetabolites				
5-FU	x [78]	x [79]	x [78]	
SERMs				
Tamoxifen		- [80]		
TKIs				
Dasatinib				
Crizotinib				

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Nilotinib				
Sunitinib				
Erlotinib				
Lapatinib		x [19]		
Ponatinib				
HDAC inhibitors				
Romidepsin	x [42]		x [42]	
Other chemotherapeutics				
ATO	x [81]	x [81]		

5-FU – 5-fluorouracil, SERMs – selective estrogen receptor modulators, TKIs – tyrosine kinase inhibitors, HDAC – histone deacetylase, ATO – arsenic trioxide.

TABLE 5.
Causes of long QT syndrome.

Congenital long QT syndromes	[82, 83]	Romano–Ward syndrome Jervell and Lange–Nielsen syndrome Andersen–Tawil syndrome Timothy syndrome
Acquired long QT syndromes	**Electrolyte dysbalancies** [82, 84, 85]	hypocalcemia hypokalemia hypomagnesemia
	Cardiac diseases [82, 84, 86]	congestive heart failure left ventricular hypertrophy myocardial ischemia myocardial infarction myocarditis bradyarrhythmia complete atrioventricular block
	Endocrine abnormalities [82, 84, 85]	hyperaldosteronism hyperparathyroidism hypothyroidism pheochromocytoma
	Intracranial disorders [82, 84, 85]	cerebrovascular accident encephalitis head injury subarachnoid hemorrhage thalamic hematoma
	Nutritional disorders [51, 82, 84]	*anorexia nervosa* liquid protein diet starvation celiac disease gastroplasty and ileojejunal bypass
	Autoimmune diseases [87]	systemic lupus erythematosus sjogren´s syndrome polymyositis/dermatomyositis systemic sclerosis rheumatoid arthritis
	Medication	see: table 1.

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CONCLUSIONS

The effect of targeted therapy on molecular properties of the heart and the development of life-threatening arrhythmias, including TdP, is probably more complex than it is generally accepted.

Cancer patients may be particularly prone to QT prolongation because they are exposed to multiple risk factors and comorbidities for developing prolonged QT interval. Identifying factors that may increase susceptibility to this abnormality and its proarrhythmic potential is of great importance. The true incidence of TdP in cancer patients with prolonged QT interval is unknown.

The level of awareness of pathophysiological mechanisms underlying delay of depolarization and repolarization (channelopathies and interstitial abnormalities) should be raised. Although targeted drugs leading to prolonged QT may possess risks of serious adverse events, the clinical benefit of therapy in the oncology setting may outweigh these effects.

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Authors' contributions:
Lucia Setteyova: 50%
Ljuba Bacharova: 20%
Beata Mladosievicova: 30%.

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