Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review

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Background—The cardiovascular complications of cancer therapeutics are the focus of the burgeoning field of cardio-oncology. A common challenge in this field is the impact of cancer drugs on cardiac repolarization (ie, QT prolongation) and the potential risk for the life-threatening arrhythmia torsades de pointes. Although QT prolongation is not a perfect marker of arrhythmia risk, this has become a primary safety metric among oncologists. Cardiologists caring for patients receiving cancer treatment should become familiar with the drugs associated with QT prolongation, its incidence, and appropriate management strategies to provide meaningful consultation in this complex clinical scenario.

Methods and Results—In this article, we performed a systematic review (using Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines) of commonly used cancer drugs to determine the incidence of QT prolongation and clinically relevant arrhythmias. We calculated summary estimates of the incidence of all and clinically relevant QT prolongation as well as arrhythmias and sudden cardiac death. We then describe strategies to prevent, identify, and manage QT prolongation in patients receiving cancer therapy. We identified a total of 173 relevant publications. The weighted incidence of any corrected QT (QTc) prolongation in our systematic review in patients treated with conventional therapies (eg, anthracyclines) ranged from 0% to 22%, although QTc >500 ms, arrhythmias, or sudden cardiac death was extremely rare. The risk of QTc prolongation with targeted therapies (eg, small molecular tyrosine kinase inhibitors) ranged between 0% and 22.7% with severe prolongation (QTc >500 ms) reported in 0% to 5.2% of the patients. Arrhythmias and sudden cardiac death were rare.

Conclusions—Our systematic review demonstrates that there is variability in the incidence of QTc prolongation of various cancer drugs; however, the clinical consequence, as defined by arrhythmias or sudden cardiac death, remains rare. (J Am Heart Assoc. 2017;6:e007724. DOI: 10.1161/JAHA.117.007724.)

Key Words: cancer therapy • cardiac arrhythmia • cardio-oncology • ECG • oncology • QT interval electrocardiography • sudden death • tyrosine kinase inhibitors • torsade de pointes

The advances in treatment of cancer have led to significant improvement in cancer-related mortality.1 Although many of the conventional drugs, such as the anthracyclines, continue to be used widely, there are many efficacious targeted therapies that are introduced into the market. An important off-target effect of some of these drugs includes abnormalities in cardiac repolarization resulting in QT prolongation. QT prolongation has been linked to an increased risk of life-threatening ventricular arrhythmia and reports of sudden cardiac death (SCD).2 Therefore, the management of the effects of cancer therapeutics on cardiac repolarization necessitates collaboration between oncologists and cardiologists. This systematic review of the literature of conventional and targeted anticancer therapies is intended to help the clinicians do the following: (1) appreciate the QT prolongation and arrhythmia potential of the many commonly used cancer drugs; (2) recognize the need for careful evaluation of the QT changes, especially in the context of other underlying ECG or
cardiac abnormalities; and (3) understand strategies to investigate and manage patients with cancer therapy–induced QT prolongation, such that the risk of SCD is not increased and potentially lifesaving cancer therapy is not withheld inappropriately.

**Clinical Perspective**

**What Is New?**

- We provide a systematic review of the available literature on corrected QT (QTc) prolongation attributable to cancer therapy.
- Any QTc prolongation is common with both conventional and targeted cancer therapy; however, the incidence of significant QTc prolongation (to >500 ms) is more common with targeted therapy.
- The reported incidence of arrhythmias and sudden cardiac death attributable to QTc prolongation from cancer therapy is extremely rare in the literature.

**What Are the Clinical Implications?**

- Our systematic review provides a reliable estimate of the risk of developing QTc prolongation for many cancer drugs that can be used to educate physicians and patients.
- When using drugs that are associated with an elevated incidence of QTc prolongation, careful monitoring is required during treatment.
- Careful evaluation with a rigorous measurement of the QT interval is an important strategy to prevent unnecessary cessation of cancer therapy and to minimize the risk of arrhythmias.
- Prompt treatment of severe QTc prolongation is needed and should be regarded as an emergency if linked with arrhythmic events or cardiac symptoms, such as syncope.

**Methods**

**Systematic Search of Cancer Therapy-Induced QT Prolongation**

**Search strategy**

Our search adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews.3 We performed a literature search with 3 databases: EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials databases (1974–December, 2015) using 3 concepts: (1) clinical trials, (2) individual anticancer drugs, and (3) cardiotoxicity. Only English-language articles were reviewed. Reference lists of individual publications and review articles were searched manually for additional studies, and drug labels of individual drugs were reviewed.

**Study selection**

Phase 1 trials evaluating the effects on QT interval of individual cancer drugs at different doses, phase 2 trials, phase 3 randomized controlled trials, and phase 4 postmarketing studies with systematic monitoring and reporting of ECG data and cardiovascular safety were considered. Prospective cohort studies were included if systematic ECG monitoring was performed. Episodes of arrhythmia or SCD were not taken into account if there was an alternative explanation for their occurrence or if there was no ECG monitoring during the study. Older clinical trials without relevant information on the QT or nonsystematic collection of ECG data were excluded (Figure 1).

**Data Management and Analysis: Data extraction**

All data were extracted by 2 cardiologists (A.P.-S. and C.G.) using predefined electronic data extraction forms, including number of subjects treated, number of subjects experiencing QT prolongation (any Common Terminology Cancer Adverse Events (CTCAE) scale version 3 grading), number of subjects experiencing grade III or more QT prolongation (ie, QT corrected prolongation of >60 ms from baseline or >500 ms), arrhythmia episodes, and SCD. No data on other cardiotoxic effects of the drugs were collected.

**Data synthesis**

The proportion of patients with QT prolongation or arrhythmia events or cases of SCD was calculated for every study. For each drug, a weighted average of the proportion of patients experiencing QT prolongation was calculated from all the studies using the number of patients treated in each study as the weighting factor.

**Results**

Our systematic search yielded 5263 articles; of those articles, 1189 full-text articles were reviewed, and 173 were finally included (Figure 1). Summary of the various cancer drugs and the incidence of QT prolongation based on our systematic review is presented in Table 1, and a classification based on incidence of corrected QT (QTc) prolongation is provided in Table 2. Additional description of commonly used agents and their impact on QTc is summarized below.

**Nontargeted Cancer Therapy**

**Arsenic trioxide**

Arsenic trioxide is used in the treatment of refractory or relapsed acute promyelocytic leukemia. The package insert reports that QTc prolongation >500 ms occurs in up to 40% of
patients. Individual cases of SCD have been described. The severity of the clinical presentation is variable, with some patients experiencing marked QTc prolongation, but QTc prolongation is not seen with oral administration. Therefore, a baseline 12-lead ECG and electrolyte levels are recommended. Concomitant QT-prolonging agents should be discontinued, and electrolytes should be normal before and during treatment. If QTc increases to >500 ms, continuation of arsenic trioxide should be carefully evaluated. QTc should be monitored at least weekly with a 12-lead ECG or with any symptoms. If a patient develops torsades de pointes (TdP) and the treatment needs to be resumed, it should be administered in a monitored unit.

**Anthracyclines (eg, doxorubicin, idarubicin, epirubicin)**

Anthracyclines are used in many common cancers. ECG monitoring was common in initial trials with only rare instances of QTc prolongation. Therefore, a baseline 12-lead ECG and electrolyte levels are recommended. Concomitant QT-prolonging agents should be discontinued, and electrolytes should be normal before and during treatment. If QTc increases to >500 ms, continuation of arsenic trioxide should be carefully evaluated. QTc should be monitored at least weekly with a 12-lead ECG or with any symptoms. If a patient develops torsades de pointes (TdP) and the treatment needs to be resumed, it should be administered in a monitored unit.

**Antimetabolites**

Fluorouracil is used in many common malignancies, such as breast and colon cancer. Its cardiotoxicity manifests as angina and coronary vasospasm. Its proarrhythmic effect is linked with ischemia. Careful assessment in 102 patients receiving fluorouracil demonstrated a mild increase in QTc (mean, 15 ms) and ventricular premature complexes on Holter monitoring. Capecitabine is a prodrug to fluorouracil. There are some isolated cases of ventricular arrhythmia related to ischemia. QTc prolongation appears to be more frequent in patients with previously known left ventricular dysfunction, previous irradiation, or trastuzumab therapy, but case reports and case series of patients presenting with acute cardiotoxicity and heart failure coupled with QTc prolongation. However, these were always in the setting of other coexisting conditions and use of other QTc-prolonging drugs.

**Figure 1.** Flow chart of articles: summary of the systematic review. CCRCCT indicates Cochrane Central Register of Controlled Trials.
| Drug Type                                | Drug                          | No. of Studies | Total No. | Range of Patients With QTc Increase, %* | Weighted Average of Patients With QTc Increase, %* | Weighted Average of Patients With QTc >500 ms, % | Arrhythmia/SCD, No. |
|-----------------------------------------|-------------------------------|----------------|-----------|----------------------------------------|---------------------------------------------------|-------------------------------------------------|--------------------|
| Antimetabolites4,5                        | Fluorouracil                  | 1              | 102       | 0                                      | 0                                                 | 0                                               | 0/0                |
|                                        | Capecitabine                  | 1              | 52        | 19                                      | 19                                                | 0                                               | 0/0                |
| Purine analogs6                         | Fludarabine                   | 1              | 56        | 0                                      | 0                                                 | 0                                               | 0/0                |
| Antimicrotubule agents7,8               | Paclitaxel                    | 3              | 290       | 1-4                                    | 2.4                                               | 0                                               | 0/0                |
| Tyrosine kinase inhibitors3-81           | Afatinib                      | 1              | 60        | 0                                      | 0                                                 | 0                                               | 0/0                |
|                                        | Afilbercept                   | 1              | 43        | 4.6                                    | 4.6                                               | 0                                               | 0/0                |
|                                        | Bosutinib                     | 2              | 87        | 0-37                                    | 11.5                                              | 0                                               | 0/0                |
|                                        | Ceritinib                     | 1              | 130       | 0.7                                    | 0.7                                               | 0.7                                             | 0/0                |
|                                        | Crizotinib                    | 2              | 101       | 0                                      | 0.9                                               | 0.9                                             | 0/0                |
|                                        | Dasatinib                     | 10 (1 with paclitaxel, 1 with ixabepilone, 1 with cetuximab) | 611 | 1.6-73 | 8.0 | 1.0 | 1/0 |
|                                        | Dovitinib                     | 2              | 49        | 3-15                                    | 8.1                                               | 4.1                                             | 0/0                |
|                                        | Imatinib                      | 5              | 897       | <0.5-6.9                                | 3.1                                               | 0.02                                            | 0/0                |
|                                        | Lapatinib                     | 2 (with trastuzumab+paclitaxel) | 117 | 1.7 | 1.7 | 1.7 | 0/0 |
|                                        | Lenvatinib                    | 2              | 319       | 0-8.1                                   | 6.5                                               | 1.2                                             | 0/0                |
|                                        | Nilotinib                     | 13             | 3076      | 0-24                                    | 2.7                                               | 0.2                                             | 0/5                |
|                                        | Nintedanib                    | 2              | 94        | 0-3.3                                   | 1.1                                               | 1.1                                             | 0/0                |
|                                        | Pazopanib                     | 3              | 99        | 0-5.9                                   | 1.0                                               | 0                                               | 0/1                |
|                                        | Ponatinib                     | 2              | 120       | 0-3.7                                   | 2.5                                               | 1.7                                             | 1/0                |
|                                        | Sorafenib/sunitinib           | 6              | 280       | 0-17.8                                  | 8.5                                               | 1.9                                             | 0/0                |
|                                        | Vandetanib                    | 32             | 2567      | 0-66.7                                  | 8.5                                               | 2.7                                             | 1/0                |
| Histone deacetylase inhibitors92-98     | Belinostat                    | 3              | 195       | 0-36.0                                  | 8.7                                               | 4.1                                             | 1/0                |
|                                        | Panobinostat                  | 10 (2 with bevacizumab, 1 with everolimus) | 654 | 0-31.4 | 4.4 | 0.7 | 0/0 |
|                                        | Romidepsin                    | 2              | 112       | 0-2.1                                   | 1.8                                               | 0                                               | 0/0                |
|                                        | Vorinostat                    | 6              | 189       | 0-35.7                                  | 12.2                                              | 3.2                                             | 0/0                |
| Proteasome inhibitor98,100              | Bortezomib                    | 2              | 22        | 0-10                                    | 4.5                                               | 4.5                                             | 0/0                |
| Vascular endothelial growth factor inhibitors101-104 | Cediranib                  | 4 (1 with FOLFOX) | 127 | 7.7-20.5 | 14.2 | 2.4 | 0/0 |
| Antiangiogenic105-109                    | Combretastatin (CA4P)         | 3              | 110       | 6.5-72                                  | 22.7                                              | 0.9                                             | 0/0                |
|                                        | Vadimezan (ASA404)            | 4              | 77        | 0-100                                   | 20.8                                              | 5.2                                             | 0/0                |
| Protein kinase C inhibitor110-114       | Enzastaurin                   | 5              | 135       | 6-24                                    | 11.8                                              | 2                                               | 0/0                |
| Monoclonal antibodies115-118            | Trastuzumab and Pertuzumab    | 4              | 167       | 0                                      | 0                                                 | 0                                               | 0/0                |

Continued
no QTc prolongation–related arrhythmias have been documented.\textsuperscript{5}

**Alkylating and alkylating-like agents and purine analogs**

Cyclophosphamide is a widely used agent with no clearly demonstrated arrhythmogenicity. Average QTc prolongation of 20 ms after high-dose cyclophosphamide added to other drugs before autologous bone marrow transplantation has been reported in a small study of patients with non-Hodgkin lymphoma.\textsuperscript{151} However, no arrhythmias were seen. Incidence of QTc prolongation with cisplatin, carboplatin, or oxaliplatin has not been reported. Effects of fludarabine were reported to be null in a series of patients.\textsuperscript{6}

**Antimicrotubule agents**

Paclitaxel is used in many malignancies, including breast, lung, and ovarian cancer. Despite a consistent bradycardic effect and orthostatic hypotension in taxane-treated patients, only mild and infrequent QTc prolongation has been reported.\textsuperscript{7,8,152}

**Targeted Cancer Therapies**

**Small-molecule tyrosine kinase inhibitors**

Small-molecule tyrosine kinase inhibitors (TKIs) are used in the treatment of hematological malignancies and solid tumors, such as renal cell carcinoma and gastrointestinal tumors. The effects of TKIs on QTc are different between agents. QTc prolongation was frequent (>5% of patients experiencing CTCAE scale grade I QTc prolongation) in patients treated with dasatinib, vandetanib, sorafenib, or sunitinib. Dasatinib is used to treat hematological malignancies and has been associated with QTc prolongation in 8% of treated patients (range, 1%–70%), but QTc >500 ms was seen only in <1%.\textsuperscript{13, 16, 20–22, 25, 32, 40, 42, 75}

Vandetanib is used to treat symptomatic or progressive medullary thyroid cancer and has a dose-dependent effect on QTc prolongation,\textsuperscript{46} affecting 15% to 20% of patients.\textsuperscript{153} Reduction of dose reverses QTc prolongation.\textsuperscript{52} A meta-analysis of 9 randomized trials with 4813 patients estimated a risk ratio for QTc prolongation versus control of 7.90 (95% confidence interval, 4.03–15.50).\textsuperscript{154} In our review, the weighted incidence of any vandetanib-related QTc prolongation was 8.6%, with QTc >500 ms in 2.6%.\textsuperscript{53–70, 153–157} Because of its long half-life (19 days), special care is needed when monitoring patients with QTc prolongation. Because of its clinical efficacy, vandetanib was approved by the Food and Drug

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**Table 1. Continued**

| Drug Type | Drug          | No. of Studies | Total No. | Range of Patients With QTc Increase, %* | Weighted Average of Patients With QTc Increase, %* | Weighted Average of Patients With QTc >500 ms, % | Arrhythmia/SCD, No. |
|-----------|---------------|----------------|-----------|----------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------|
| B-Raf inhibitor\textsuperscript{119,120} | Vemurafenib   | 2              | 3597      | 0–6.5                                  | 2.2                                           | 1.8                                           | 2/0                 |
| Other\textsuperscript{121–136} | Arsenic trioxide | 15            | 533       | 0–38                                   | 22.0                                          | 5.8                                           | 24/1                |

FOLFOX indicates folinic acid, fluorouracil, and oxaliplatin; QTc, corrected QT; and SCD, sudden cardiac death.

*Common terminology cancer adverse events scale grade ≥1.

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**Table 2. Classification of the QTc Prolongation Potential Cancer Drugs Based on Our Systematic Review**

| Classification          | Drug                  |
|-------------------------|-----------------------|
| High risk (>10% incidence) | Arsenic trioxide Bosutinib Capcetabine Cediranib Combretastatin (CA4P) Enzastaurin Vadimezan Vinostatin |
| Moderate risk (5%–10% incidence) | Belinostat Dasatinib Dovitinib Lenvatinib Sorafenib Sunitinib Vandetanib |
| Low risk (1%–5% incidence) | Aflibercept Imatinib Lapatinib Nilotinib Nintedanib Paclitaxel Panobinostat Ponatinib Romidepsin Vemurafenib |
| Very low risk (<1% incidence) | Anthracyclines Fluorouracil Aflatalin Centiniib Crizotinib Fludarabine Pazopanib Pertuzumab Trastuzumab |

QTc indicates corrected QT.
Administration for human use in 2012, but with safe prescription strategies that include obtaining a baseline ECG and at 2 to 4 and 8 to 12 weeks after starting the treatment and every 3 months thereafter.\textsuperscript{158}

Sorafenib and sunitinib are used for the treatment of advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and gastrointestinal stromal tumors. QTc prolongation of <10 ms was observed in a small study with sorafenib.\textsuperscript{41} A carefully performed study of cardiac safety in patients receiving sorafenib and sunitinib showed an incidence of QTc prolongation of any degree of 9.5% among 86 patients.\textsuperscript{34,159} No episodes of TdP were reported. Sunitinib has a dose-dependent effect on QTc prolongation. Subsequent trials with sunitinib with cardiac safety monitoring have reported an average incidence of QTc prolongation of any degree of 8.5% and a QTc >500 ms of 1.7% without any arrhythmia.\textsuperscript{15, 23, 28, 37}

Nilotinib is approved for chronic myelogenous leukemia (Philadelphia chromosome positive). It is known to prolong QTc, with 5 cases of SCD reported in 867 patients treated in initial trials leading to a warning in the Food and Drug Administration labeling. Two subsequent phase 2 studies and one retrospective analysis showed that 2% to 8% of patients have a >60-ms increase in QTc from baseline, with 1.2% developing a QTc of >500 ms,\textsuperscript{27,160} without any cases of SCD. The weighted proportion of QTc prolongation of any grade with nilotinib was 2.7% with QTc of >500 ms, seen in 0.3% of cases. Caution and periodic ECG monitoring are advised when using nilotinib.\textsuperscript{71, 73, 74, 76, 77, 79, 80} QTc prolongation was common (37%) in patients with hepatic impairment treated with bosutinib,\textsuperscript{10} but this was not seen in other smaller studies.\textsuperscript{11, 12} QTc prolongation was infrequent or absent with afatinib, crizotinib, ceritinib, dovitinib, imatinib, lapatinib, lenvatinib, nilotinib, pazopanib, and ponatinib.\textsuperscript{9, 14, 16, 17, 19, 24, 26, 27, 29–33, 35, 36, 38, 39, 72, 78, 81, 161–164}

**Monoclonal antibody–based TKIs**

For trastuzumab, despite its known effects on left ventricular ejection fraction, no relevant changes to QTc have been documented.\textsuperscript{117, 118, 165} Similarly, pertuzumab has not shown QTc effects.\textsuperscript{115, 116} Bevacizumab has been used alone or in combination with other TKI and other chemotherapeutic agents without causing QTc prolongation, despite its cardiotoxicity potential.\textsuperscript{166–169}

**Histone deacetylase inhibitors**

This class of drug is used in the treatment of hematological malignancies, such as T-cell lymphomas and multiple myeloma. The prevalence of QTc prolongation is frequent (10%–15%) in patients treated with vorinostat\textsuperscript{94–98,170} and belinostat.\textsuperscript{171–173} Other histone deacetylase inhibitors, including panobinostat (used for multiple myeloma)\textsuperscript{92–91} and romidepsin,\textsuperscript{92, 93, 174} have a lower incidence of QTc prolongation (≈1%).

**Proteasome inhibitors**

Bortezomib used in the treatment of multiple myeloma is the only proteasome inhibitor that has been associated with QTc prolongation of >500 ms in 1 patient in a pooled analysis of 2 studies involving 22 patients treated with bortezomib in combination with other chemotherapy.\textsuperscript{99, 100}

**Vascular endothelial growth factor (VEGF) inhibitors and vascular disruptors**

These drugs are used in the treatment of various solid malignancies. Among the identified studies, QTc prolongation was seen in 14% of patients treated with cediranib\textsuperscript{101–104} and 21% of patients treated with vadimezan (ASA404).\textsuperscript{108, 109, 175} Caution and periodic ECG monitoring is advised during the treatment with these agents. Affibercept was also associated with a small proportion of QTc prolongation (5%) in one study.\textsuperscript{29} The effect of QTc prolongation of combretastatin-A4 has been consistently shown in the literature, but no TdP events have been reported.\textsuperscript{106, 107} The incidence of QTc prolongation during infusion seems to be dose dependent and seems to affect virtually all patients treated, with increases of as much as 37 ms in patients treated at higher doses (80 mg/m²).\textsuperscript{105, 176, 177} However, this drug has not been approved for therapeutic use at present.

**Protein kinase C inhibitors**

Enzastaurin is a serine/threonine kinase inhibitor that targets protein kinase C and protein kinase B pathways. It is now in phase 3 trials and has antitumoral activity in non–small-cell lung cancer. On the basis of phase 1 and 2 studies, QTc prolongation occurs in 12% of treated patients. No reports about arrhythmia have been published, but careful use is recommended with periodic monitoring of ECGs.\textsuperscript{110–114}

**BRAF inhibitors**

Data from patients with metastatic melanoma treated with vemurafenib show QTc prolongations in 3.2% on average and QTc >500 ms in 2.3%, with only 0.06% incidence of arrhythmias.\textsuperscript{119, 120}

**Mechanisms of Drug-Induced QTc Prolongation**

The molecular mechanisms of QTc prolongation with many cancer drugs are not known. Interaction with the normal function of one of the potassium channel proteins of the cardiomyocytes (human Ether-a-go-go (hERG)) seems to be
the cause of QTc prolongation for arsenic trioxide and TKIs.\textsuperscript{178} For histone deacetylase inhibitors, whether the QTc prolongation is attributable to inhibition of hERG or other mechanisms is unknown. Concomitant use of drugs that inhibit the metabolism of the cancer drugs can also prolong QTc (eg, inhibitors of cytochrome P450 3A4 [CYP3A4] enzymes [herbal products, azole fungi, macrolides, and certain HIV medications] and CYP2D6 enzymes [eg, fluoxetine]). Alternatively, conditions that prevent elimination pathways of cancer drugs can prolong QTc (eg, renal and liver failure). There is also a potential for genetic predisposition to drug-induced QTc prolongation,\textsuperscript{179} although specific associations have not been established for cancer therapeutics.

Discussion: Management of Patients at Risk or With Cancer Therapy–Related QT Prolongation

On the basis of our systematic review and our clinical experience, a suggested management approach for patients scheduled to start potential QT-prolonging cancer therapy or for patients with QT prolongation during cancer treatment is described later and summarized in Figure 2.

Precancer Treatment Assessment and Prevention

In patients scheduled to receive potential QT-prolonging cancer drugs, a complete medical and medication history (including nonprescription, recreational, and complementary/alternative medicines) should be obtained. In cancer patients being evaluated for clinical trials (before the start of cancer therapy), the prevalence of prolonged QTc has been reported to be \( \approx 6\% \).\textsuperscript{180–182} Therefore, a pretreatment ECG should be performed to document QTc values. A risk score to identify individual patient-specific risk of QTc prolongation during cancer therapy does not exist.

Appropriate measurement of QTc

Measurement of the QT should be based on leads that normally show the earliest QRS onset and the latest end of the T wave (T-wave offset), which are II and V5. The end of the QT interval is the point at which the T wave reaches the isoelectric line. A normal QTc interval is \( >350 \) and \( <450 \) ms in adult men and \( >360 \) and \( <460 \) ms in adult women. Because the QT interval is inversely proportional to heart rate (HR), different formulas have been described to correct the QT interval for the HR. The objective of calculating the QTc is to obtain a patient’s QT corrected to an HR of 60 beats per minute (bpm) which equals to an R interval to R interval (RR) time of 1000ms. The Bazett formula (\( \text{QTcB} = \frac{\text{QT}}{\sqrt{\text{RR}}} \)) and the Fridericia formula (\( \text{QTcF} = \frac{\text{QT}}{\sqrt{\text{RR}}} \)) are based on the assumption of an exponential relationship between QT and the beat to beat interval (RR interval). This relationship is less precise for fast HRs and, hence, other formulas were suggested as alternatives, especially for faster HR (\( >90 \) bpm): the Framingham formula\textsuperscript{183} (\( \text{QTcFram} = \text{QT} + 0.154 \times (1 - \text{RR}) \)), assuming a linear relationship, and the Hodges formula (\( \text{QTcH} = \text{QT} + 1.75 \times (\text{HR} - 60) \)).\textsuperscript{184} The Bazett and Fridericia formulas are used most commonly, but evidence supports correcting QT with the Hodges formula to be more accurate, especially at an HR \( >90 \) bpm.\textsuperscript{185} When an intraventricular conduction delay, left bundle branch block, right bundle branch block, or paced rhythm (usually adopting left bundle branch block—like morphological features) is present, a modified QT interval can be calculated by subtracting 48.5% of the duration of the QRS from the measured QT (\( \text{mQT} = \text{QT} - 0.485 \times (\text{QRS}) \)) and then correcting it for HR with conventional formulas or by taking a QTc of \( >550 \) ms as abnormal without any substraction.\textsuperscript{186} Subtracting the QRS duration from the QT measurement (ie, calculating the so-called JT interval) and using a cutoff of \( >360 \) ms is an alternative to the modified QT interval calculation.\textsuperscript{187} Most ECG machines automatically report a QT interval by calculating the time between the earliest QRS onset of all leads and the latest offset of the T wave. As a result, the automatic QT interval is often longer than the QT interval from any individual lead. Also, automated measurements have not been validated in conduction abnormalities (eg, left bundle branch block) and, hence, manual measurement is the only option. Figure 3 provides useful examples of QT measurement and corrections in several ECG scenarios. It is our suggestion that the QTc calculation can be performed accurately with HR between 60 and 90 bpm with both Bazett and Fridericia formulas and that for HR \( >90 \) bpm, the Hodges correction is the most widely accepted. When a broad QRS of \( >120 \) ms (bundle branch block or conduction delay) is present using a QTc of \( >550 \) ms as a cutoff for abnormality is acceptable, but if baseline QTc is at the upper end of normal or for QRS that is wide but \( <120 \) ms, it is our advice to use the modified QT interval (see above) for a more precise and reproducible measurement.

Identifying causes and risk for QT prolongation

If patients have QTc prolongation, correctable causes should be identified. First, electrolytes should be measured and any abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) should be corrected before treatment. Patients with cancer specifically are at risk for electrolyte imbalance, especially during cancer treatment, because of the following: (1) poor oral intake and conditions that promote loss of potassium and/or magnesium, like salt-losing nephropathy secondary to platinum salts; (2) diarrhea or emesis from mucositis; (3) fever with sweating; (4) treatment with laxatives; (5) alcohol abuse; and (6) treatment with corticosteroids. Drugs with potentially synergistic effects with cancer therapy to prolong QTc should be
identified and modified or stopped. Table 3 provides a selective list of commonly used noncancer treatment drugs that prolong QTc and some safer alternatives, and an exhaustive list can be obtained from http://crediblemeds.org and is updated frequently.\textsuperscript{188} Other causes of baseline QTc prolongation include structural heart disease\textsuperscript{189} and genetic inherited arrhythmias, including Brugada syndrome, congenital long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. These patients should be evaluated by a cardiologist or cardiac electrophysiologist before cancer therapy with potential QT-prolonging drugs. A comprehensive review of all medications that need to be avoided or the strategy for monitoring during the treatment should be defined carefully in these patients before cancer therapy.\textsuperscript{190}

**Patient counseling and monitoring**

Patients should be counseled about worrisome cardiac signs after starting the treatment (syncope, presyncope, fainting, rapid palpitations, or dizzy spells) that should prompt them to
seek medical evaluation. With respect to early detection, ECGs should be repeated during treatment, as per drug labels. ECG monitoring after a change in dose of a QTc-prolonging drug is recommended. However, because experience with some of the newer cancer drugs is limited, if concern for QTc prolongation exists, an ECG should be performed after every treatment cycle and when the plasma concentration of the drug reaches a steady state (eg, 5 half-lives). The duration of monitoring will depend on the half-life of all implicated drugs and the impairment in the elimination pathways. In hospitalized patients, if available, a QT-alert system could be used to identify those who prolong their QTc during cancer treatment. This has been shown to be effective in the detection of patients (cancer and noncancer) at risk of TdP. Strategies to minimize the risk of cancer therapy–related QTc prolongation are summarized in Table 4.

Management of QTc Prolongation

When a prolonged QTc interval is detected (>500 ms or an increase of >60 ms longer than baseline), the patient should be evaluated carefully, with discontinuation of all offending drugs immediately (if appropriate). Strategies previously discussed to identify causes of QTc prolongation should be considered. Patients who experience associated syncope, palpitations, or QTc >500 ms and/or bradycardia (HR, <60 bpm) should be evaluated immediately in a monitored setting. An ECG should be repeated every 24 hours until resolution of QTc prolongation is confirmed. A prolonged QTc increases the risk of a potentially lethal ventricular arrhythmia called TdP (Figure 4A). Most of the data on the risk of TdP in relation to QTc prolongation are from large registries of patients with congenital long QT

Figure 3. Examples of QT measurement and correction (QTc). ECG strips from lead II recorded at 25 mm/s and at 1 mm/mV with the measurement of the QT interval highlighted and calculations of different corrected measures: Bazett formula (QTcB), Hodges formula (QTcH), and Fridericia formula (QTcF). A correction with the Hodges formula is exemplified here: QTcH=QT+1.75×[heart rate (HR)/60]. A, A normal ECG with narrow QRS and a normal QT interval [QTcH=380+1.75×(71–60)=399 ms]. B, A narrow QRS with prolonged QT interval [QTcH=500+1.75×(57–60)=495 ms]. C, An example of a wide QRS because of a biventricular paced rhythm (note 2 small pacing spikes preceding the QRS) that falsely prolongs QT [QTcH=480+1.75×(83–60)=520 ms, final QTc=QTcH−180×0.5=430 ms]. D, A wide QRS as a result of a left bundle branch block [LBBB; QTcH=400+1.75×(74–60)=424 ms, final QTc=QTcH−120×0.5=364 ms]. E, A patient with a prolonged PR interval of 360 ms with the P wave overlapping with the T-wave recording; drawing an imaginary line following the downslope of the T wave is the accepted way of calculating the T-wave offset and, thus, the end of the QT interval [QTcH=380+1.75×(62–60)=393 ms]. F, A patient with junctional bradycardia, where the T wave is followed by a subsequent wave (U wave) that should not be included in the QT measurement [QTcH=390+1.75×(98–60)=426 ms].
These data show that each 10-ms increase in QTc contributes approximately a 5% to 7% increase in risk for cardiac events, including syncope, cardiac arrest, and/or death. Other risk factors for TdP beyond QTc have been described in settings outside of cancer therapy (Table 5) and, thus, the extrapolation to the cancer population is less clear. Although some medications are associated with QTc prolongation, not all drugs that prolong the QTc cause TdP. Therefore, the risk assessment of TdP attributable to drugs should not only be based on QTc alone but considered in the context of other predisposing TdP risk factors. Recurrence of TdP is frequent and, hence, the occurrence of a single event mandates urgent clinical evaluation and monitoring.

Drugs for correcting prolonged QTc should be started if worrisome ECG signs of TdP exist (eg, frequent ventricular premature beats or short runs of nonsustained ventricular tachycardia) or if TdP develops (asymptomatic or symptomatic). Premonitory and worrisome signs for TdP are prolonged QTc (>500 ms), severe aberration of the T-U segment, beat-to-beat instability (more marked aberration of the T wave after a long R-R interval), and/or frequent ventricular premature beats (Figure 4B). Patients with such abnormalities should be admitted to a cardiac care unit. The first-line treatment is magnesium sulfate, given intravenously with repeated doses if signs of electric instability persist. Next is the initiation of a β-adrenergic drug, such as isoproterenol, titrated to obtain an HR of >100 bpm with careful evaluation.

### Table 3. Noncancer Drugs Known to Cause QTc Prolongation

| Risk               | Drug Categories                                      | Common Antibacterial and Antifungal Drugs | Prokinetic and Antiemetic Drugs | Antipsychotics | Antidepressants |
|--------------------|------------------------------------------------------|------------------------------------------|---------------------------------|----------------|----------------|
| Known risk         | Antiarrhythmic Drugs                                 | Amiodarone, Disopyramide, Dofetilide, Dronedaron, Flecaïnide, Ibutilide, Procainamide, Quinidine, Sotalol | Moxifloxacin, Levofloxacin, Ciprofloxacine, Clarithromycin, Erythromycin, Azithromycin, Fluconazole, Pentamidine | Domperidone, Chlorpromazine, Ondansetron, Droperidol | Haloperidol, Mesoridazine, Thioridazine, Pimozide |
|                    | Possible risk                                        | Telavancin, Telithromycin, Gemifloxacin, Norfloxacin, Ofloxacin | Dolasetron, Granisetron, Promethazine, Tropisetron | Lithium, Clozapine, Paliperidone, Risperidone, Promethazine, Perphenazine, Pimavanserin, Iloperidone, Aripiprazole, Azenapine | Clomipramine, Desipramine, Imipramine, Mirtazapine, Nortriptyline, Trimipramine, Venlafaxine |
| Conditional risk   | Ivabradine                                           | Amphotericin B, Itraconazole, Ketoconazole, Metronidazole, Posaconazole, Voriconazole, Cotrimoxazole (avoid in congenital long QT syndrome) | Metoclopramide | Quetiapine, Olanzapine, Ziprasidone | Amitriptyline, Doxepin, Fluoxetine, Fluvoxamine, Paroxetine, Sertaline, Trazadone |
| Alternatives       | Penicillin, Cephalosporins, Doxycycline, Anidulafungin | Aprepitant, Fosaprepitant, Palonosetron | Brexiprazole | Desvenlafaxine, Bupropion (except in supratherapeutic dose) | Vorl©xetine, Vilazodone, Levomilnacipran, Milnacipran |

Known risk of torsades de pointes (TdP): These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. Possible risk of TdP: These drugs can cause QT prolongation but lack evidence for a risk of TdP when taken as recommended. Conditional risk of TdP: These drugs could cause TdP only under certain conditions, such as excessive dosing, electrolyte imbalance, and interacting with other drugs that can cause TdP. Alternatives: Drugs that at this point have not been linked to clinically significant QTc prolongation. Please see http://crediblemeds.org for an exhaustive list. QTc indicates corrected QT.
of the response, because patients with inherited congenital long QT syndrome could experience worsening symptoms. The role of antiarrhythmic therapies is less well established, but in case of refractory TdP, lidocaine infusion can be considered.\textsuperscript{197}

Temporary ventricular or atrial pacing at 100 to 120 bpm should be considered if the patient is refractory to the previous measures. If the patient has a preexisting pacemaker or implantable cardioverter defibrillator system, changes in the lower rates can have the same protective effects. This measure leads to the disappearance of virtually all ventricular arrhythmias.\textsuperscript{198}

### Specialist Consultation

Cardiology and/or cardiac electrophysiology (EP) consultation is specifically advised in the following: (1) patients seen with a markedly prolonged QTc interval (>500 ms); (2) those receiving treatment with a known QTc-prolonging drug, who experience symptoms suggestive of being of cardiac origin; and (3) those with known inherited arrhythmia disorders. Patients who experience associated syncope or presyncope suspected to be of cardiac origin, rapid palpitations, or QTc prolongation with new-onset bradycardia (HR <60 bpm) and a high degree of heart block (second and third degree) are at high risk for repeated episodes and should be in a monitored setting with specialist consultation.\textsuperscript{199}

### Long-Term Treatment

No recommendations on the role of cardiac implantable device insertion exist to date. Patients with severe bradycardia secondary to cancer therapy who are candidates for a QTc-prolonging drug may benefit from a dual-chamber pacemaker insertion to avoid symptomatic sinus bradycardia or sinus pauses that are risk factors for TdP. An implantable cardioverter defibrillator should be considered as follows: (1) if the life expectancy of the patient is >1 year, (2) if the patient has experienced resuscitated SCD, or (3) if the patient has experienced severe arrhythmia from a known QTc-prolonging agent without any correctable cause and no alternative cancer treatment is available. These patients require careful individual evaluation and discussion in a multidisciplinary team to ensure that the risks and benefits of implantable cardioverter defibrillator therapy are considered.

#### Table 4. Summary of Strategies to Minimize Cancer Therapy–Related QTc Prolongation and Risk of TdP\textsuperscript{190}

1. Avoid use of QTc-prolonging drugs in patients with pretreatment QTc >450 ms
2. Discontinue QTc-prolonging drug(s) if QTc interval prolongs to >500 or >550 ms if a baseline widening of QRS is present (>120 ms secondary to pacing or bundle branch block)
3. Reduce dose or discontinue QTc-prolonging drug(s) if the QTc increases ≥60 ms from pretreatment value
4. Maintain electrolytes (serum potassium, magnesium, and calcium) concentration within normal range
5. Avoid important known drug interactions
6. Adjust doses of renally eliminated QTc-prolonging drugs in patients with acute kidney injury or chronic kidney disease
7. Avoid rapid intravenous administration of QTc-prolonging drugs
8. Administration of >1 drug with the potential to prolong the QT interval should be avoided
9. Avoid use of QTc-prolonging drugs in patients with a history of drug-induced TdP or those who have previously been resuscitated from an episode of SCD
10. Avoid use of QTc interval–prolonging drugs in patients who have been diagnosed as having one of the congenital long QT syndromes
11. Monitor ECG with frequency, depending on ongoing therapy, drug concentration, and dose changes of QTc-prolonging therapy

QTc indicates corrected QT; SCD, sudden cardiac death; and TdP, torsades de pointes.
Also, the potential to turn off active implantable cardioverter defibrillator therapy if and when a patient reaches the palliative stage should be discussed.

**Limitations**

The translation of findings of QTc prolongation or associated arrhythmias from clinical trials from which our data are obtained to clinical practice is challenging. Most of the clinical trials of new cancer therapies in this review excluded patients with a baseline pre-treatment QTc >450 ms, carefully followed up patients with repeated ECGs, or avoided the use of concomitant QTc-prolonging drugs. Therefore, findings from such trials may not be generalizable to clinical practice, where such meticulous follow-up may not be offered. Therefore, care must be taken in patients receiving potentially QTc-prolonging drugs in routine clinical practice. Because our search was exhaustive, cancer therapies that are not listed in Table 1 are unlikely to cause clinically relevant QTc prolongation. However, because of the rapid pace of new drug discovery in the field of oncology, it is possible that new therapies causing QTc prolongation have been introduced into the market during the preparation of this article. Regardless, the concepts of diagnosis and management of QTc prolongation remain the same.

**Conclusions**

Patients with cancer receiving treatment are prone to QTc prolongation because of many risk factors and comorbidities. The true incidence of QTc prolongation and TdP from the multitude of cancer drugs is challenging to determine. In patients treated with conventional cancer drugs, the weighted incidence of any QTc prolongation in our systematic review varied between 0% and 22%, although QTc >500 ms, arrhythmias, or SCD was extremely rare. The risk of QTc prolongation with targeted therapies was also variable (0%–22.7%), with severe prolongation (QTc >500 ms) reported in 0% to 5.2% of the patients. However, arrhythmias and SCD were rare. Strategies to prevent QTc prolongation and the risk of subsequent TdP involve identification of potential drug interactions, correction of underlying electrolyte abnormalities, careful ECG monitoring, and patient education.

**Table 5. Clinical Risk Factors of TdP**

| Categories              | Examples                                      |
|-------------------------|-----------------------------------------------|
| Congenital              | Congenital long QT syndrome                   |
| Physiological           | Female sex, bradycardia, baseline QT prolongation |
| Structural heart disease| Myocardial ischemia, congestive heart failure, hypertrophic cardiomyopathy |
| Electrolytes            | Hypokalemia, hypomagnesemia, hypocalcemia     |
| Drugs                   | Digitalis therapy, other noncancer QT-prolonging drugs (Table 3) |
| Arrhythmias             | Recent conversion to sinus rhythm from atrial fibrillation with a QT-prolonging drug (eg, amiodarone or dofetilide) |
| Other                   | Liver or renal dysfunction, hypothyroidism, hospitalization, intensive care unit stay |

TdP indicates torsades de pointes.

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