Are We Too Focused on the QT Interval with Oncology Treatments?
Position – Yes

Michael G. Fradley, MD
Director, Cardio-Oncology Program
Associate Professor of Medicine
University of South Florida and Moffitt Cancer Center
Global Cardio-Oncology Summit 2018
September 28, 2018
Attest that

**Michael Fradley**

Has met the requirements of this board
and is hereby certified as a diplomate in

**Clinical Cardiac Electrophysiology**

Ongoing certification is contingent upon meeting the requirements of Maintenance of Certification.
Please visit www.abim.org to verify current certification status.

**TEST COMMITTEE ON CLINICAL CARDIAC ELECTROPHYSIOLOGY**
Fundamental Argument

• QT interval assessment and monitoring is important

• Current practice of QT evaluation in oncology makes no sense
  • Reliance on different correction formulae
  • Lack of standardized maximum QTc values
  • Lack of standardized screening recommendations

• Over-aggressive screening can lead to potential harm
  • Increased health care costs
  • Patient stress
  • Unnecessary withholding of potentially life saving cancer treatments.
Hi Dr. Fradley,

Dr. Kim is wondering if you can re-calculate this patient’s QTc intervals by hand and see whether either value will come below 450.

Please let me know.

Thanks,

Taymeyah
Are We Good at Measuring the QT Interval?

Viskin et al. *Heart Rhythm*. 2005; 2: 569-574
QT Measurement

[Diagram showing QRS and QT intervals]
Key Points for Accurate QT Measurement

- Measure Longest QT interval
- Average measurement over several beats
- Utilize tangent method to determine the end of the T wave
- Avoid measuring U waves in most circumstances
- During atrial fibrillation, average the QT interval over 10 beats
- Utilize the JT interval in patients with bundle branch blocks or ventricular pacing
- Manually verify electronic QT measurements

## Corrected QT Measurement

<table>
<thead>
<tr>
<th></th>
<th>Bazett</th>
<th>Fridericia</th>
<th>Framingham</th>
<th>Hodges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mathematical Formula</strong></td>
<td>( QT_c = QT/(RR^{1/2}) )</td>
<td>( QT_c = QT/(RR^{1/3}) )</td>
<td>( QT_c = QT + 0.154(1,000-RR) )</td>
<td>( QT_c = QT + 1.75(HR-60) )</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td>Non Linear</td>
<td>Non Linear</td>
<td>Linear</td>
<td>Linear</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Simple; most widely used in practice</td>
<td>More accurate at slower HR (risk of TdP is greater at slower HR)</td>
<td>Adaptable across genders; population based formula</td>
<td>Useful with multiple populations</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Overcorrects at fast HRs and undercorrects at slow HRs;</td>
<td>Overcorrects at high HRs</td>
<td>Uncertain validity in populations other than Framingham Heart Study; Overcorrects at high HRs</td>
<td>Less correlation with HR variability; Overcorrects at high HRs.</td>
</tr>
</tbody>
</table>

Why Do We Care About the QT Interval?

• The QT interval is a measure of ventricular depolarization and repolarization

• Normal QT intervals:
  • Males: <470ms
  • Females: <480ms

• Significant QT prolongation (>500ms) can be marker for increased risk for ventricular arrhythmias

An Historical Digression...
Why Do We Care About the QT Interval?

Drug Induced QTc >500ms: RR of arrhythmia is 1.2

Untreated Stage IV Cancer: RR of death is ∞
QT Prolongation In Cancer Patients Is Common...

• Moffitt Cancer Center:
  • 35% of patients had QT prolongation using the Bazett formula
  • 15% using the Fridericia formula

But...clinically significant events defined by arrhythmias or sudden cardiac death were rare (under 1%)

• MD Anderson:
  • Approximately 20% of patients screened for a clinical trial had QT prolongation

• Meta-analysis:
  • Severe prolongation (QTc >500 ms) reported in up to 5.2% of the patients treated with targeted therapies.

Porta-Sanchez et al. J Am Heart Assoc. 2017. doi: 10.1161/JAHA.117.007724
QT Interval Prolongation in the Cancer Patient

CO-EXISTING CONDITIONS
- Older age
- Female
- Hypothyroid
- Congenital Long QT Syndrome
- Cardiac disease
- LV dysfunction
- cardiac ischemia
- bradycardia
- other conduction disease

CANCER THERAPY
- taxanes
- cyclophosphamide
- epothilones
- thalidomide
- interferons
- interleukin-2
- multi-targeted tyrosine kinase inhibitors
  - sunitinib
  - dasatinib
  - vandetanib*
- arsenic trioxide
- tipifarnib*
- enzastaurin*
- combretastatin*
*not FDA approved

CANCER THERAPY-RELATED
- dehydration/electrolyte imbalance
  - nausea and emesis
  - diarrhea
  - diuresis
  - poor oral intake
- renal insufficiency
- hepatic dysfunction
- poorly controlled diabetes

CONCOMITANT MEDICATIONS
- antidepressants
- anti-emetics
- antibiotics
- antipsychotics
- antifungals
- antihistamines
- methadone

QT Interval Assessment in Oncology Clinical Trials

Why are multiple sets of replicate ECGs obtained at different times points in oncology clinical trials?

A. To Improve Patient Safety
B. To Reduce Sample Size
C. To establish pharmacokinetic parameters
D. I don’t know – seems like non-sense to me!
• Spontaneous QT interval variability is common

• Replicate ECGs reduces sample size

• Replicate ECGs improves within-subject QT variability...to a point...

QT Interval Assessment in Oncology Clinical Trials: Significant Attention But No Standardization

Borad et al. *Invest New Drugs.* 2013; 31: 1056-65
# QT Interval Assessment: Significant Attention But No Standardization

<table>
<thead>
<tr>
<th>Drug</th>
<th>ECG at Baseline</th>
<th>Follow Up ECGs</th>
<th>Baseline QTc</th>
<th>QTc Requiring Dose Adjustment/Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>Yes</td>
<td>7 days after starting or with dose increase; repeat 3-6 months</td>
<td>Not listed</td>
<td>Dose adjustment and/or cessation if QTcF ≥480ms</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>Yes</td>
<td>ECG at baseline and day 14 of first cycle, beginning of second cycle and then as clinically indicated</td>
<td>QTcF≤450ms</td>
<td>Dose adjustment and/or cessation if QTcF ≥480ms</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Yes</td>
<td>Check ECG at baseline, 2-4 weeks and 8-12 weeks after starting and then every 3 months.</td>
<td>QTcF≤450ms</td>
<td>Dose adjustment and/or cessation if QTcF ≥500ms</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Yes</td>
<td>Prior to first cycle, 7-30 days after starting therapy or after any dose change, 3-6 months to ensure stability (may consider more frequently if hepatic impairment).</td>
<td>QTc&lt;500ms</td>
<td>Dose adjustments and/or cessation if QTc &gt;500ms</td>
</tr>
</tbody>
</table>

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QT Prolongation and Adverse Outcomes

QT/TdP Risk Categories for Drugs

- **Known Risk of 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** currently lack evidence for a risk of TdP when taken as recommended.

- **Conditional Risk of TdP** - These drugs are associated with TdP **BUT** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

- **Drugs to Avoid in Congenital Long QT Syndrome (cLQTS)** - These drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories (KR, PR & CR) **PLUS** additional drugs that do not prolong the QT interval per se but which have a Special Risk (SR) because of their other actions.
QT Prolongation and Adverse Outcomes

Known Risk of TdP: These drugs prolong the QT **AND** are clearly associated with a known risk of TdP, even when taken as recommended:

- Arsenic
- Vandetinib
# QT Prolongation and Adverse Outcomes: Arsenic

APML remission rates with arsenic 85-93%

- QT interval prolongation can be substantial
- Clinically relevant arrhythmic events <1%

<table>
<thead>
<tr>
<th>Correction Factor</th>
<th>QT &gt; 470ms</th>
<th></th>
<th>QT &gt; 500ms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Peak Arsenic Level</td>
<td>Baseline</td>
<td>Peak Arsenic Level</td>
</tr>
<tr>
<td>Uncorrected QT, ms</td>
<td>386±35</td>
<td>0</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Bazett-correction QT, ms</td>
<td>441±28</td>
<td>15</td>
<td>102</td>
<td>90</td>
</tr>
<tr>
<td>Fridericia-correction QT, ms</td>
<td>422±25</td>
<td>5</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>Hodges-corrected QT, ms</td>
<td>421±23</td>
<td>5</td>
<td>70</td>
<td>62</td>
</tr>
<tr>
<td>Sagie-corrected QT, ms</td>
<td>421±24</td>
<td>4</td>
<td>60</td>
<td>53</td>
</tr>
</tbody>
</table>

# QT Prolongation and Adverse Outcomes

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>Epirubicin</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>5FU</td>
<td>Ribociclib</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Lapatinib</td>
<td>Romidepsin</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Lenvatinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Cabecitabine</td>
<td>Leuprolide</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Midostaurin</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Crizotinib</td>
<td><strong>Nilotinib</strong></td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Osimertinib</td>
<td>Vorinostat</td>
</tr>
<tr>
<td>Dasatinib</td>
<td><strong>Panobinostat</strong></td>
<td></td>
</tr>
</tbody>
</table>

Possible Risk of TdP: These drugs prolong the QT but lack evidence for a risk of TdP when taken as recommended.
QT Prolongation and Adverse Outcomes: Nilotinib

- 458 clinical trial patients
- Median QT prolongation 10ms
- 4 patients with QTcF >500ms (0.8%)
- ΔQTcF >60ms in 18 patients (4%)
- No Torsdade de Pointes
- Sudden Cardiac Death 0.3%

Tasigna (nilotinib) [package insert]. Basel: Novartis Pharmaceuticals, Switzerland: 2018
Conclusions

• QT interval evaluation is important

• Over-evaluation can have significant adverse effects

• Rational and standardized approaches to QT assessment must be implemented
Thank You