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Cardio-oncology (MG Fradley, Section Editor)

QT Interval Prolongation Associated With Cytotoxic and Targeted Cancer Therapeutics

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Opinion statement

Cardiovascular toxicities are potentially serious treatment limiting complications of many different cancer therapeutics including traditional cytotoxic chemotherapies as well as targeted- and immunotherapies. As a result, there is increased monitoring for cancer treatment-related cardiotoxicities, ranging from heart failure to arrhythmias. Many anticancer treatments are known to prolong the QT interval through a variety of mechanisms including direct effects on ion channels and indirectly via intracellular signaling pathways. While QT prolongation increases the risk for the potentially life-threatening ventricular arrhythmia torsades de pointes, the incidence of this arrhythmia in the setting of most cancer treatments is quite rare, and the majority of patients can continue safely receiving these medications despite their QT prolonging potential. A multidisciplinary approach to the cardiovascular care of the cancer patient is essential to mitigate risk of cardiotoxicity while minimizing unnecessary treatment disruption of potentially life-saving cancer treatments.

Introduction

The oncologic therapeutic landscape has significantly changed over the last several decades with the advent of targeted- and immunotherapies leading to significantly improved outcomes for many malignancies when

compared to standard cytotoxic chemotherapy. Nevertheless, significant cardiovascular side effects have been identified, ranging from heart failure to arrhythmias. There is increasing concern about the effects of oncologic therapeutics on cardiac repolarization, manifesting as QT prolongation, which increases the risk of developing torsades de pointes (TdP), a potentially lethal type of polymorphic ventricular tachycardia. Unfortunately, the QT interval is a relatively poor surrogate for determining risk of TdP and few other effective methods exist to assess the likelihood of developing these arrhythmias. Despite the significant attention paid to this potential cardiotoxicity, actual arrhythmic event rates remain extremely low especially if reasonable risk mitigation strategies are implemented. As such, close cooperation between cardiologists and oncologists is of vital importance to minimize the likelihood of developing drug-induced QT prolongation, while ensuring the continued delivery of optimal and potentially life-saving cancer treatments.

QT interval—basic electrophysiology

The QT interval is the electrocardiographic manifestation of cellular depolarization and repolarization of the myocardium. This electrical process, known as an action potential, is controlled by channels that regulate the inward and outward flow of ions across the myocardial cell membrane. Depolarization occurs with the rapid influx of sodium and calcium ions while repolarization is primarily due to efflux of potassium ions. QT prolongation results from alterations to the normal functioning of these membrane ion channels. In particular, a reduction in repolarizing current or amplification of depolarizing current can delay the action potential and thereby lengthen the QT interval [1].

The action potential is divided into five phases. Depolarization occurs during phase 0 and is driven by the opening of Na^+ channels. This is followed by phase 1 during which the rapid transient outward flow of K^+ ions leads to early repolarization. Phase 2 represents the plateau phase resulting from the balance between inward calcium and outward potassium flow. Rapid depolarization occurs during phase 3 of the action potential, with the activation of rapid delayed rectifier potassium channels (IK_r). Finally, phase 4 represents a return to baseline resting membrane potential [2, 3].

QT interval—evaluation and measurement

In general, a normal QT interval length is between 350 and 450 ms in adult men and between 360 and 470 ms in adult women. A QT interval greater than the 99th percentile should be considered abnormally prolonged (> 470 ms in males and > 480 ms in females). Regardless of sex, a QT interval of > 500 ms is considered significantly abnormal and is associated with an increased risk of arrhythmia [4].

The QT interval is measured on the surface electrocardiogram (ECG) from the beginning of the QRS complex to the termination of the T wave. Accurate measurement of the QT interval can be quite challenging even for cardiologists. This was illustrated in a study comparing a group of arrhythmia experts, general cardiologists, and internists ability to accurately calculate the QTc interval. While > 80% of arrhythmia experts were successful in their evaluation, over 50% of internists and over 40% of general cardiologists inaccurately measured the QT length [5•]. Manual calculation is often essential as electronic ECG

machine calculations are frequently inaccurate [2]. Typically, automated QT intervals are determined by time of earliest QRS onset in any lead to the end of the most delayed T wave in any lead. This frequently results in a longer QT interval when compared to utilizing one specific lead [6•]. It is recommended to measure the longest QT interval on a surface ECG, generally lead II or V5 as they typically have the earliest QRS onset and latest T wave endpoint. Additionally, the measured interval ideally should be averaged over 3–5 beats especially if sinus arrhythmia is present [2].

It can be especially challenging to accurately determine the end of T wave. The preferred technique involves drawing a tangential line to the steepest slope of the descending limb of the T wave. The point at which it intersects with the isoelectric line constitutes the appropriate end of the T wave [7]. Additionally, measurement of the QT interval should not include U waves unless there is clear fusion present [2].

Atrial fibrillation (AF) and wide QRS complexes, such as those seen with bundle branch blocks or ventricular pacing, complicate the ability to accurately assess the QT interval. In the setting of atrial fibrillation, the RR interval irregularity can lead to substantial beat to beat QT interval variability. One recommendation is to average QTc measurements over at least 10 beats. An alternative option is to average the QT interval associated with the longest and shortest RR interval. Wide QRS complexes frequently result in prolonged QT interval measurements primarily from delays in depolarization as opposed to repolarization. Some experts recommend calculation of the JT interval (subtraction of QRS length from QT interval) as a potentially more reliable estimate [8]; however, routinely utilizing this method in the clinical setting may be impractical especially for non-cardiologists. Given these challenges, it may be reasonable to avoid QT-prolonging drugs if the QTc is > 500 ms regardless of the QRS duration [1, 2].

It is well recognized that heart rate impacts the QT interval such that at slower rates the QT is longer, and at faster rates the QT is shorter. The QT interval should ideally be calculated and compared to a heart rate of 60 beats per minute (bpm). Different correction formulae have been proposed to standardize the QT interval across the range of heart rates (Table 1). The Bazett (QTcB) and Fridericia (QTcF) formulae are the most commonly used correction methods in clinical practice and drug development. Both formulae are derived from mathematical modeling techniques. Of the two, the Bazett formula (QT interval divided by the square root of the RR interval) is utilized more frequently; however, it is also associated with significant error, overcorrecting at faster heart rates, and undercorrecting at slower heart rates when TdP is most likely to occur. In a study evaluating the rates of cancer clinical trial eligibility based on QTc values, significantly more patients were unnecessarily excluded if the Bazett formula was utilized as compared to other methods [9]. The Fridericia formula (QT interval divided by the cubed root of the RR interval) also overcorrects at faster heart rates (but to a lesser extent than the Bazett) and is more accurate at slower heart rates. The Framingham Linear Regression Equation [10] and the Hodges formula assume a linear relationship between QT interval and RR interval which allow for better measurements at these elevated heart rates. Unfortunately, the Framingham and Hodges calculations are quite cumbersome, making them challenging to utilize in clinical practice. Moreover, the Framingham equation is derived from empiric epidemiologic

Table 1. Common QT correction formulae [3, 12]

	Bazett	Fridericia	Framingham	Hodges
Mathematical formulae	$QTc = QT / (RR)^{1/2}$	$QTc = QT / (RR)^{1/3}$	$QTc = QT + 0.154 \times (1 - RR)$	$QTc = QT + 1.75 \times (\text{Heart Rate} - 60)$
Advantages	Most commonly used in clinical practice; simple calculation	More accurate at slower heart rates; simple calculation	Accuracy especially in large populations and faster heart rates	Accuracy especially in large populations and faster heart rates
Disadvantages	Overcorrects at fast HRs and under corrects at slow HRs	Overcorrects at fast HRs	Complicated calculation. Unclear validity for individuals or populations outside of original study population	Complicated calculation. Unclear validity in individuals

data and may be of more use when evaluating large populations rather than individual patients. While none of these methods have been directly compared to determine which is most accurate at predicting TdP, the Fridericia formula is frequently recommended in the cancer population over the Bazett formula [2, 3, 11].

Risk factors for QT interval prolongation

Numerous pharmaceuticals, from antibiotics to antineoplastic agents, are known to prolong the QT interval, most commonly via direct inhibition of the HERG subunit of the IK_r channel. It should be noted however that compared to traditional pharmaceuticals, anticancer drugs such as tyrosine kinase inhibitors (TKIs) prolong the QT interval via their effects on intracellular signaling, primarily through inhibition of the phosphoinositide 3-kinase (PI3K) signaling pathway, which has downstream effects on many ion channels including decreasing IK_r and increasing late sodium (INa-L) currents. Despite these effects, drug-induced TdP generally occurs when numerous other patient-related or acquired risk factors are present [12, 13].

Multiple genetic conditions (long QT syndromes [LQTS]) are known to affect the QT interval. The most common LQTS genotypes result is decreased function of outward potassium channels or enhanced function of inward sodium channels. Specifically, LQTS-1 and LQTS-2 lead to a loss of function of the IK_s channels and IK_r channels, respectively, while LQTS-3 results in gain of function of the I_{Na} channel. Other forms of LQTS are frequently related to abnormalities in proteins associated with ion channel trafficking or function [14, 15].

In addition to pharmacologic and genetic factors, increasing age [16] and female gender [17] are associated with QT prolongation. After puberty, men have shorter QT intervals than women, which may be a result of testosterone production. With age, the QT interval gradually increases for both men and women possible resulting from changes in sex hormone production [18–22]. In addition, female hearts have fewer ion channels, which increases susceptibility

to repolarization abnormalities [23]. In fact, it is reported that 70% of TdP occurs in females [24, 25]. Electrolyte abnormalities (hypomagnesemia and hypokalemia), cardiovascular diseases (including bradycardia, left ventricular hypertrophy, and cardiomyopathy), intracranial pathology [26], HIV infection, hypothermia, and connective tissue disorders are also associated with QT interval prolongation [3]. There are also reports of autoimmune myocardial channelopathies leading to QT interval prolongation [27].

Cancer therapeutic associated QT prolongation

Oncology patients frequently have baseline prolonged QT intervals. In a study from MD Anderson evaluating over 8000 ECGs in patients enrolled in phase 1 clinical trials, 20% demonstrated QT interval prolongation, but episodes of TdP were exceedingly rare [28•]. The observed QT prolongation is due to many of the aforementioned factors; however, cancer therapeutics including traditional cytotoxic chemotherapies as well as targeted agents have been implicated for their potential to prolong the QT interval (Table 2).

Cytotoxic chemotherapy

Arsenic trioxide

Arsenic's medicinal properties were first identified in China over 2000 years ago; however, the toxicity profile of arsenic significantly limited its use. In the 1990s, arsenic trioxide was shown to have significant benefit in the treatment of acute promyelocytic leukemia (APL) [29], with complete remission rates reported between 85 and 93% [30–33]. Despite its anticancer efficacy, QT prolongation is common and ventricular arrhythmias have been reported especially in the setting of arsenic overdose [34]. Arsenic leads to ventricular repolarization abnormalities via IK_r and IK_s blockade as well as reducing HERG protein expression [35–37].

Although early studies of arsenic trioxide at treatment doses for APL suggested only minor ECG changes, subsequently a number of case reports of TdP in patients taking arsenic trioxide [31, 38–40] led to more systematic studies that have better defined arsenic-associated cardiotoxicity. In a small Japanese study ($n = 8$), all patients treated with arsenic trioxide demonstrated QT prolongation on continuous ECG monitoring during drug infusion; however, no episodes of TdP were observed [41]. A larger study of 99 patients from phase 1 and phase 2 arsenic trials reported QT prolongation in 38% of participants, with 26% having a QTc interval of more than 500 ms. Notwithstanding, only one patient experienced TdP in the context of concurrent severe hypokalemia [42]. In a different study evaluating serial ECGs from 113 patients treated with arsenic for non-APL malignancies, QT prolongation was identified in 26% of patients; however, only 12% experienced a QTc of more than 500 ms and no clinically significant cardiac arrhythmias were reported [43].

Despite the effect arsenic has on the QT interval, the overall risk of arsenic-induced TdP remains quite low, especially in absence of other QT prolonging risk factors. Nevertheless, the FDA has issued a black box warning for arsenic-induced QT interval prolongation and TdP. Current labeling recommends halting therapy if the QT interval prolongs to 500 ms with resumption once the

Table 2. QTcF monitoring regimens based of FDA recommendations for select cancer therapeutics

Cancer therapeutic	Class	Average studied incidence of QTcF increase	Baseline QTcF for initiation	Recommended monitoring algorithm	QTcF threshold for dose adjustment
Arsenic trioxide [6•, 44]	Cytotoxic	22%	< 500 ms	Baseline ECG. Weekly ECG while receiving infusions thereafter	> 500 ms; consider dose adjustment or cessation until QTcF returns to < 460 ms
Nilotinib [6•, 76]	TKI	2.7%	< 450 ms	Baseline ECG. Repeat ECG 7 days after starting or with dose increase; repeat 3–6 months	> 480 ms; consider dose adjustment or cessation until QTcF returns to < 450 ms
Sunitinib [6•, 81]	TKI	8.5%	Not listed; caution if prolonged	Baseline ECG. Periodic ECG monitoring as clinical warranted	Not listed; consider if QTc > 500 ms
Vandetanib [6•, 82]	TKI	8.5%	< 450 ms	Baseline ECG. Repeat at 2–4 weeks and 8–12 weeks after starting and then every 3 months	> 500 ms; consider dose adjustment or cessation until QTcF returns to < 450 ms
Vemurafenib [6•, 127]	TKI (BRAF)	2.2%	< 500 ms	Baseline ECG. Repeat 7–30 days after starting therapy or after any dose change and at 3–6 months to ensure stability. May consider more frequently if hepatic impairment	> 500 ms; upon recovery to QTc < 500 ms, restart at a reduced dose. Permanently discontinue if the QTc remains > 500 ms and increased > 60 ms from pre-treatment values
Panobinostat [6•, 140]	HDI	4.4%	< 450 ms	Baseline ECG. Periodic ECG monitoring as clinical warranted	> 480 ms; consider dose adjustment or cessation until QTcF returns to < 450 ms
Ribociclib [154]	CDK4/6 Inhibitor	Unknown	< 450 ms	ECG at baseline, at day 14 of the first cycle, at the beginning of second cycle and then as clinically indicated	> 480 ms

QT interval is less than 460 ms [44]. The development and implementation of these simple and effective cardiovascular risk mitigation strategies has allowed for the continued and safe administration of arsenic trioxide to treat APL and other malignancies [3, 45].

Anthracyclines

Anthracyclines are a group of cytotoxic chemotherapeutic agents including daunorubicin, doxorubicin, idarubicin, and epirubicin, used in the treatment of multiple malignancies including leukemia, lymphoma, sarcoma, and breast cancer. Anthracyclines are most associated with the development of left ventricular dysfunction and heart failure [46] though arrhythmias are increasingly recognized. Cardiotoxicities occur either from structural changes in the setting of cardiomyopathy or through direct cardiac myocyte toxicity [47, 48]. Initial trials did not report significant QT prolongation [49–56]; however, several subsequent studies have suggested otherwise. For example, in a study of non-Hodgkin's lymphoma patients treated with epirubicin, all participants experienced some degree of QT prolongation, with dexrazoxane attenuating these effects [57]. In a study from Finland, 18% of patients exposed to doxorubicin demonstrated QTc prolongation of more than 50 ms from baseline values [58]. In a Brazilian study of breast cancer patients, the QTc interval was significantly prolonged after anthracycline exposure compared to baseline values (439.7 ± 33.2 vs. 472.5 ± 36.3 ms, $p = 0.001$) [59]. Despite the QTc prolonging potential of anthracyclines [59], there does not appear to be an excess risk of TdP with these therapies [6•, 47].

5-Fluorouracil

5-Fluorouracil (5-FU) is an antimetabolite used primarily in gastrointestinal malignancies including colon and esophageal cancer. While the primary cardiotoxicity of 5-FU is coronary vasospasm and associated ischemia, mild QTc prolongation of approximately 15 ms has been reported [60–62]. Capecitabine is an oral cancer therapeutic that is metabolized into 5-FU, with similar associated cardiotoxicities. Ventricular arrhythmias have been reported, primarily in the context of ischemia; however, QTc prolongation has been described in the setting of other predisposing factors including left ventricular dysfunction, previous irradiation, or trastuzumab therapy [6•].

Tyrosine kinase inhibitors

Abnormal signaling pathways play an important role in many different cancers, frequently resulting from aberrant activity of protein kinases. TKIs specifically target these proteins and have led to significantly improved outcomes in the treatment of many different solid and hematologic malignancies [63]. Unfortunately both on-target and off-target cardiovascular complications have been identified. QTc prolongation is of particular concern with the FDA issuing standard or black box warnings for multiple agents; however, this does not appear to be a class-related effect [6•, 64]. QTc prolongation has been reported with bosutinib [65], dasatinib [66–76], nilotinib [77], osimertinib [78–80], sorafenib [81], sunitinib [82], and vandetanib [83]; however, there is a lack of evidence of QT prolonging potential with afatinib [84], brigatinib [85],

crizotinib [86, 87], ceritinib [88], dovitinib [89–91], imatinib [71, 92, 93], lapatinib [94, 95], larotrectinib [96], lenvatinib [97, 98], nintedanib [99], pazopanib [100], and ponatinib [101]. Monoclonal antibody TKIs including trastuzumab [102–104], pertuzumab [103, 105], and bevacizumab [106–109] have little documented effects on the QT interval despite other associated cardiotoxicities [6•].

Nilotinib

Nilotinib is a small-molecule TKI approved for first- or second-line treatment of Philadelphia chromosome-positive (BCR-ABL) chronic myeloid leukemia (CML). QT prolongation with nilotinib is relatively mild. In healthy volunteers, the mean QT interval change was 18 ms, with less than 1% experiencing a QTc of more than 500 ms. In clinical trials, QT interval changes were reported between 5 and 15 ms and 2–8% of patients demonstrated a QT interval change of more than 60 ms. In 458 clinical trial patients (CML-chronic phase and CML-accelerated phase) treated with 400 mg twice daily nilotinib, QTcF ≥ 500 ms was observed in 4 individuals and a change in QTcF ≥ 60 was seen in 18 patients [110]. Sudden cardiac death was reported in 0.3% of patients treated with nilotinib. As a result of these collective data, the FDA issued a black box warning for QT prolongation and sudden cardiac death for nilotinib [77]. It should be noted however that preceding QT interval prolongation was not definitively documented in the patients experiencing sudden death. Moreover, there is now increasing recognition that nilotinib is associated with other cardiotoxicities including myocardial infarction, stroke, and peripheral arterial disease which may have contributed to the reported episodes of cardiac death [111, 112]. Nevertheless, current recommendations recommend periodic ECG monitoring with consideration of dosage adjustment or cessation if the QTc > 480 ms [79].

Sunitinib

Sunitinib is a small-molecule TKIs that affects the vascular endothelial growth factor receptor (VEGFR), platelet-derived grown factor (PDGFR), as well as c-kit signaling. It is used primarily in treating gastrointestinal stromal tumors, renal cell carcinoma, and hepatocellular carcinoma as well as FLT3+ acute myeloid leukemia. In a series of studies [113–117], the incidence of QTc prolongation was 8.5%, with an average QTc > 500 ms occurring in 1.7% of patients without any notable episodes of TdP or sudden cardiac death [6•]. Additional focused studies on sunitinib-associated cardiovascular toxicities reported a similar 9.5% incidence of QTc prolongation. The mean increase in the QTc with sunitinib, calculated using the Fridericia formula, is 15.4 ms [118–120]. Of note, sunitinib-induced QTc prolongation may be dose-dependent [3, 121]. QTc prolongation may be related to both direct inhibition of the HERG subunit as well as decreased PI3K signaling pathway activity within cardiac myocytes [122].

Vandetanib

Vandetanib is a small-molecule TKI that affects VEGFR-2, RET, and endothelial growth factor receptor (EGFR) used primarily in the treatment of medullary

thyroid cancer. QTc prolongation is well-described with vandetanib and it currently carries an FDA black box warning for QTc prolongation and sudden cardiac death [83]. Vandetanib is felt to have a dose-dependent effect on the QT interval [6•, 123–125]. One meta-analysis of nine randomized clinical trials reported a relative risk of 7.9 for QTc prolongation with vandetanib ($p < 0.00001$) with an incidence of all-grade QT prolongation events reported at 16–18% [126]. In a report by Porta-Sanchez et al. [6•], the weighted incidence of vandetanib-induced QTc prolongation was 8.6% with a QTc > 500 ms of 2.6%. It is recommended to check an ECG at baseline, at 2–4 and 8–12 weeks after starting the drug and then every 3 months thereafter. Moreover, the drug should not be initiated if the QTcF is > 450 ms at baseline, and dose adjustment and/or cessation should occur if the QTcF is > 500 ms [83].

Vemurafenib

Vemurafenib is a BRAF inhibitor used in the treatment of metastatic melanoma. Several studies have illustrated vemurafenib-induced QTc prolongation [6, 127, 128]. A recent large multi-center study of 3219 vemurafenib-treated patients with a median follow-up time of 33.1 months reported QTc prolongation in 523 (16%) of patients, with Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 prolongation occurring in 52 patients (2%). Despite this, no clinically significant arrhythmias were observed [129]. Current recommendations are to check an ECG prior to the first cycle, 7–30 days after starting therapy or after any dose change, and 3–6 months after starting treatment to ensure stability. More frequent evaluations can be considered in the setting of hepatic impairment. Dose adjustments and/or cessation should be considered if the QTc exceeds 500 ms [128].

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDI) are a class of therapeutics that modulate the posttranscriptional activity of proteins by inactivating histone deacetylase enzymes eventually leading to apoptosis. These are primarily used in the treatment of hematologic malignancies such as T cell lymphomas and multiple myeloma. QTc prolongation has been reported with multiple HDIs. The mechanism for QTc prolongation may be due to the structural similarities of the histone deacetylase enzyme and the HERG channel [3, 130]. Both vorinostat [131–135] and belinostat [136–138] are well-documented to have QTc prolongation averaging between 10 and 15% [6•]. Romidepsin is also associated with QT prolongation. Despite reports of sudden cardiac death, a direct causal link of these events with preceding QT prolongation has not been established [139, 140]. Panobinostat is an HDI used in the treatment of multiple myeloma. Panobinostat has a FDA black box warning for severe and fatal cardiac ischemic events and arrhythmias; however, there is little data to suggest associated QTc prolongation. In the initial trials, arrhythmias occurred in 12% of patients and cardiac ischemia in 4% of patients [6•, 141]. Although the incidence of QTc prolongation is reported at only 1% and no reported QTc-associated TdP episodes [142–145], serial ECG monitoring is still recommended with interruption of therapy if QTc > 480 ms.

CDK4/6 inhibitors

Cyclin-dependent kinase (CDK) dysregulation or inhibition is an identified mechanism of cancer cell proliferation, and is a target for anticancer therapeutics [146]. Ribociclib is cyclin D1/CDK4/6 inhibitor and is approved for the treatment of hormone receptor (HR)-positive, HER2-negative advanced, or metastatic breast cancers. While the initial trials showed great clinical promise, there were concerns over QTc prolongation associated with this agent. In the initial phase I trials [147–149], QT prolongation was shown to be dose-dependent and reversible upon cessation of agent [149]. One study showed prolongation in 9% of patients treated at the recommended initial dose, with up to 33% of patients demonstrating QT lengthening at doses above > 600 mg/day [149]. In the MONALEESA-2 trial, an increase in the QTc of more than 60 ms from baseline was identified in 3% of the patients treated with ribociclib, and 3.6% of the patients had an average QTc interval of more than 480 ms [152]. Although no episodes of TdP were reported [150–154], the current recommendation is to obtain an ECG at baseline, at day 14 of the first cycle, at the beginning of second cycle and then as clinically indicated. Therapy should not be initiated if the QTcF is > 450 ms, and it should be held or stopped if the QTcF lengthens to more than 480 ms [155]. Despite these finding, QTc prolongation does not appear to be a class-related effect as other CDK 4/6 inhibitors including palbociclib and abemaciclib are not associated with significant QTc changes [156].

Conclusion

Abnormalities in repolarization leading to QTc prolongation are a significant cardiotoxicity of both traditional cytotoxic chemotherapies as well as novel targeted therapeutics. QT prolongation is often augmented by the presence of other pharmaceuticals or patient specific factors. Despite the relatively rare occurrence of associated TdP and sudden cardiac death, close monitoring and clinical awareness are necessary to minimize the risk of these life-threatening outcomes. Close cooperation between cardiologists and oncologists can lead to the development of thoughtful risk mitigation strategies allowing the majority of patients to safely receive these potentially life-saving cancer treatments.

Compliance with Ethical Standards

Conflict of Interest
Sanjay Chandrasekhar declares that he has no conflict of interest.
Michael G. Fradley has received compensation from Novartis for service as a consultant.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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