Letters to the Editor

Consideration of QT/QTc Interval Data in a Phase I Study in Patients with Advanced Cancer.

To the Editors: We commend the effort of these authors to undertake and report on their analysis of the QT/QTc interval during their phase I evaluation of combretastatin A4 phosphate and also for their inclusion of these data in this publication (1). Capturing and interpreting such data can be challenging, especially in the context of a phase I oncology study. Therefore, several aspects of this report deserve additional comment.

Study Eligibility. Unlike phase I studies performed in normal volunteers, first-in-human studies conducted in patients with cancer are often designed to provide at least some opportunity for disease control. Should baseline QTc/QTc measurements or other cardiovascular parameters exclude a patient with advanced cancer from such a first-in-human study when preclinical studies suggest that QT prolongation is a potential liability? In the study by Cooney et al. (1), eligibility criteria specified a “normal 12-lead ECG, reviewed by a cardiologist within 2 weeks of entry.” It would be of great interest to understand how many patients were excluded based on cardiac findings, including QTc. A small study of electrocardiogram assessments in cancer patients reported that 36% of patients have abnormalities at baseline, including sinus tachycardia, bundle branch block, ST-T wave abnormalities, atrial fibrillation, and prior myocardial infarction (2). In addition, it has been anecdotally reported that ~14% of cancer patients have a prolonged QTc at baseline. However, the confounding effects of age, concomitant medicines, and underlying illnesses have not been clearly defined (3, 4). We need to more thoroughly explore the baseline cardiac characteristics of cancer patients so that relevant restrictions on eligibility can be carefully applied. Minimizing the number of patients excluded from participation in cancer clinical trials in which they may derive therapeutic benefit, while still ensuring safety, remains a high priority in oncology.

Variability in QT/QTc. Understanding the intrapatient daily variability in QTc is an obvious and important factor when defining what change in QTc (for an individual patient) will prompt concern or modify intended dose delivery. In a methodology study with 12-lead electrocardiograms in 32 healthy volunteers (16 males, 16 females, mean age = 38 years), the QTcF (QT corrected by the Fridericia formula) varied over the 12-hour study day by an average of 37 milliseconds (range, 8 to 112 milliseconds; ref. 5). Although the daily variability in QTc of cancer patients has not been well described, it may be even larger because cancer patients are likely to have advanced age, concomitant medical problems and are likely to be taking concomitant medications. To reduce intrapatient variability and measurement error, it has been recommended that the baseline QTc be rigorously investigated and be expressed as the mean (or median) of multiple electrocardiogram assessments, sometimes including a match in time to account for potential diurnal variation (6).

Correction of QT for Heart Rate. The Bazett and the Fridericia formula are commonly used for correction of the QT interval for heart rate with the choice typically based on characteristics of the compiled data set. For example, it is known that the Bazett formula results in overestimation of the QTc at high heart rates, and the higher the heart rate, the greater the overestimate. In the study by Cooney et al. (1) in which the Bazett formula was used, almost all of the patients had heart rates ≥ 60 bpm (23 of 25 at baseline and 24 of 24 at 4 hours), and furthermore, 11 of 24 patients had a heart rate of ≥100 bpm at 4 hours. Using the reported heart rate and uncorrected QT, we calculated the QTc using the Fridericia formula. The mean value at 4 hours after dose was 420 milliseconds, a difference of 17.5 milliseconds compared with baseline (402.5 milliseconds) as compared with their report of a more significant change (30.8 milliseconds) by the Bazett formula. Again, because the majority of the measured heart rates were ≥60 bpm, the Bazett correction may have significantly overestimated the QTc response at 4 hours. Because the optimal approach for correction depends on the data observed in the study, it is fortunate that these investigators also collected heart rate, uncorrected QT, and RR interval data, thus allowing for supplemental analyses. As the authors point out, understanding of clinical significance of their QTc findings is further complicated by lack of a placebo-controlled treatment group, recognizing that placebo administration is commonly not acceptable to patients with advanced cancer who volunteer for phase I clinical studies (7).

Despite the inherent clinical trial limitations of measuring effects of drugs on QT interval, Cooney et al. achieved their study objectives and treated patients safely with a drug that likely prolongs QTc. In summary, this work adds to a new and growing experience in cancer drug development that suggests ECG monitoring can be incorporated into oncology studies to evaluate potential QT liabilities. Furthermore, the postapproval experience with arsenic trioxide, a drug known to prolong the QT interval, indicates that monitoring and risk management strategies can be designed and successfully implemented by practicing oncologists (2). Clearly, such liabilities should not broadly preclude development of promising new anticancer compounds. However, relative to studying potential QT prolongation in the context of cancer clinical trials, continued research is indicated to identify relevant inclusion/exclusion criteria, to determine criteria for treatment discontinuation, to identify better study designs and methodologies for QT testing, and finally, to better characterize risk-benefit considerations relative to potential QT liability and potential anticancer efficacy.
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In Response: We greatly appreciate the thoughtful comments and important insight into the challenges of electrocardiographic (ECG) monitoring and cardiac side effects that may be encountered in early phase I trials of novel antinecancer agents outlined in the commentary by Varterasian et al. (1). They rightly point out that patients with advanced cancer are often older and therefore more likely to be receiving concomitant medications for underlying illnesses that may confound the true cardiac side effect profile of a novel antineoplastic agent. The initial requirement for a normal ECG “signed off by a cardiologist at baseline” was prompted by the putative mechanism of action of the drug, which is a vascular targeting or, perhaps preferably, vascular disrupting agent. The true selectivity of combretastatin A4 phosphate for tumor vasculature could not be excluded on the basis of observations in preclinical animal toxicology studies and tumor blood flow models (2). Although an analogue of combretastatin A4 phosphate, combretastatin B1, is a HERG-type K⁺ channel blocker and prolongs action potential duration, the cardiac electrophysiologic effects we observed with combretastatin A4 phosphate, in retrospect, were not fully anticipated upon the launch of this first time in humans phase I study in cancer patients. The clinical toxicity we encountered over the course of our study was consistent with an agent that is vascularexically active, substantiated by vasomotor type reactions, changes in hemodynamic parameters, abdominal and tumor pain, and cardiac ischemia (2). Patients were excluded for our study at entry because of abnormalities on their baseline ECG, which we did not prospectively track. We chose to correct the QT interval for changes in heart rate using the Bazett formula because this is the calculation most commonly used in clinical practice and is frequently used in clinical investigational trials despite its known limitations (3, 4).

We entirely agree with the comments of Varterasian et al. on the variability in QT/QTc, correction of QT for heart rate, and limitations of using the Bazett formula. Specifically, Bazett’s formula overcorrects the QT interval at fast heart rates and undercorrects it at low heart rates. The QT is negatively correlated with heart rate, and Bazett’s formula overcorrects for this by yielding a positive correlation (i.e., a situation where higher heart rates yield higher corrected QT intervals and lower heart rates yield smaller corrected QT intervals). Fridericia’s formula appears advantageous because it leaves the corrected QT interval uncorrected with heart rate. The value of any QT measure rests, however, not with its correlation to heart rate or lack thereof but rather with its correlation to clinical toxicity. In this regard, Bazett’s metric may have as much discriminatory power as Fridericia’s metric (5).

The data in our study suggest that combretastatin A4 phosphate has the potential to prolong Bazett’s QTc and ventricular repolarization. However, use of this agent can be done safely with appropriate surveillance and monitoring. Interestingly, the increase in heart rate observed following combretastatin may fortuitously afford protection against proarrhythmia associated with prolongation of ventricular repolarization. Torsade des pointes is associated with slow heart rates and typically occurs after bradycardic pauses. In conclusion, as we proceed with further clinical development of this compound in the phase II setting, patients are required to have normal ECGs, no history of coronary artery disease, normal left ventricular function, serum K⁺ and Mg²⁺ are monitored, and serial ECGs are obtained over the first 4 hours after infusion over the first several cycles of treatment. These safeguards are prudent, given what we presently understand about the cardiovascular safety profile of this compound while at the same time provides cancer patients with opportunities to receive a novel agent, which may ultimately prove efficacious.

Mary Varterasian
Howard Fingert
Marilyn Agin
Mark Meyer
Pfizer Global Research and Development
Ann Arbor, Michigan
New London, Connecticut

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Matthew Cooney
Tomas Radivojevitch
Afshin Dowlati
Beth Overmoyer
Nathan Levitan
Kelly Robertson
Scot C. Remick
Developmental Therapeutics Program
CASE Comprehensive Cancer Center
University Hospitals of Cleveland and
CASE School of Medicine
Cleveland, Ohio

Bruce S. Stambler
Division of Cardiology
University Hospitals of Cleveland and
CASE School of Medicine
Cleveland, Ohio

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Limitations of the Adenoma–Carcinoma Sequence in Colorectum

To the Editors: There is clearly a need to identify reliable endpoints in cancer prevention trials (1). However, the limitations of the adenoma-carcinoma model in the colorectum are underappreciated. The fact that colorectal adenomas may progress to cancer is beyond dispute. Far less clear is the proportion of colorectal cancers (CRCs) that develops within a preexisting adenoma. Increasingly, there is evidence of alternative pathways to CRC implicating lesions other than traditional adenomas (2). Of special importance in this regard are the serrated polyps initiated by mutation of BRAF and having extensive DNA methylation (3). Of greater concern in the context of using adenomas as surrogates for CRC is the fact that adenomas outnumber CRCs by approximately 30 to 1 (4). One can deduce that an individual adenoma has an extremely low probability of evolving into a CRC within the average human life span. Support for this observation is provided by the disappointingly small effect of adenoma removal in the course of three large and protracted population-based randomized controlled trials of fecal-occult-blood testing (5–7). By virtue of the design of these trials, study-group patients had far more endoscopies and instances of polypectomy than did control-group patients. Yet the main benefit from the increased investigation of the study group subjects was not a reduction in the incidence of CRC but the detection of CRC at an early stage (and, therefore, a reduced mortality). Additionally, longitudinal observational studies have demonstrated that colorectal adenomas show very limited growth with time, except in patients with a family history of colorectal neoplasia (8, 9).

It is often argued that the demonstration of particular genetic profiles within stages of the adenoma–cancer sequence provides absolute proof that this sequence serves as the evolutionary pathway for CRC in the “vast majority” of cases. It is generally acknowledged that mutation of APC, K-ras, and p53 are the cornerstones of this pathway. In fact, only 7% of CRCs have all three mutations, an observation that forces us to question the existence of a dominant linear model of colorectal tumorigenesis and to accept that CRC is very much a multipathway disease (10). Investigation of unselected series of primary CRC indicates that APC mutation occurs in approximately 60% (11) of cases and that K-ras mutation and p53 mutation are inversely related (10). Artificial inflation of the frequency of the APC mutation figure is explained by overreliance on nonrepresentative cancer cell line data, underrepresentation of proximaly located CRC, or the assumption by APC interest groups that mutations must occur in APC even though they cannot be detected (an analogy with the Emperor’s new clothes). The 40% gap is not filled by β-catenin, which is mutated only in a subset of CRCs in hereditary non-polyposis CRC (HNPPC; ref. 11, 12). A further serious concern with respect to regarding adenomas as surrogates for CRCs is the vast difference in the rate of malignant conversion of adenomas in different clinical conditions. In familial adenomatous polyposis, many thousands of colorectal adenomas have developed by the second decade, whereas the mean age for developing CRC is ~40 years. One can estimate that the risk of malignant progression for an individual adenoma is about 1 in 1000. By contrast the risk of malignant transformation of an adenoma in HNPPC is not only around unity but occurs within a short time frame (13). An intermediate position is observed in the case of sporadic colorectal neoplasia. Importantly, the adenomas in these three clinical scenarios cannot be distinguished morphologically despite having vastly different natural histories. Conceivably, the latter observation is explained by differing frequencies of genetic instability at the somatic level. Whatever the reason, one can conclude that the clinical behavior of an individual adenoma is highly unpredictable and that this fact will limit the usefulness of the colorectal adenoma as a surrogate for CRC in trials of chemoprevention.

Jeremy R. Jass
Department of Pathology
McGill University
Montreal, Quebec, Canada

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surrogate end points for colorectal cancer (CRC), worthy of consideration in evaluating colorectal adenomas as hereditary non-polyposis colorectal cancer (Lynch syndrome). Lancet 13. Vasen HFA, Nagengast FM, Meera Khan P. Interval cancers in epithelium to adenocarcinoma is well documented (5—10). Subjects with high-risk adenomas have been characterized—based on the number, size, and architecture of adenomas, as well as on family and personal history of adenomas and CRC and on the presence of germ-line lesions, such as the adenomatous polyposis coli gene (Apc) mutations defining familial adenomatous polyposis (11). The ability to define such high-risk cohorts is a key factor in designing successful studies for evaluation of drugs to prevent colorectal cancer.

We agree with Dr. Jass that the available evidence does not yet support the use of earlier histologic lesions (e.g., aberrant crypt foci) or the presence of a few specific genetic lesions (e.g., ras, Apc, or p53) as surrogate end points. We recognize and agree that neoplastic progression is multipath and results in increasing cellular disorganization, dysfunction, and heterogeneity. Adenomas, like other intraepithelial neoplasia, are chosen as the optimal surrogate end point because they reflect the process of neoplastic progression and encompass the multiplicity of possible neoplastic events (7—9). We expect that at some point in the future, genomic and proteomic analyses will allow development of molecular profiles that better define subgroups at high risk of neoplastic progression in the colorectal epithelium, and that parallel or surpass adenomas in utility as surrogate end points.

The purpose of our article (4) is to define an effective strategy for clinical development of drugs to prevent colorectal cancer. The clear public health need for this strategy is evidenced by the estimated CRC incidence and death rate for the United States in 2004 of 150,950 and 57,310, respectively (12). Although we are mindful of Dr. Jass’s concerns, the factors that he cites do not diminish the utility of adenomas as end points in this endeavor.

Gary J. Kelloff
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Bethesda, Maryland

Richard L. Schilsky
Biological Sciences Division
University of Chicago
Chicago, Illinois

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Mary Vartarian, Howard Fingert, Marilyn Agin, et al.


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