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Safety Biomarkers and the Clinical Development of Oncology Therapeutics: Considerations for Cardiovascular Safety and Risk Management

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Abstract

During the clinical development of oncology therapeutics, new safety biomarkers are being employed with broad applications and implications for risk management and regulatory approval. Clinical laboratory results, used as safety biomarkers, can influence decision making at many levels during the clinical development and regulatory review of investigational cancer therapies, including (1) initial eligibility for protocol therapy; (2) analyses used to estimate and characterize the safety profile; and (3) treatment delivery, based on specific rules to modify or discontinue protocol treatment. With the increasing applications of safety biomarkers in clinical studies, consideration must be given to possible unintended consequences, including (1) restricted access to promising treatments; (2) delays in study completion; and (3) limitations to dose delivery, escalation, and determination of the maximal tolerated dose, the recommended phase 2 dose, and the optimal biologic dose selected for registration studies. This review will compare and contrast 2 biomarkers for cardiac safety that are employed in an increasing number of clinical programs designed for investigational oncology therapeutics: (1) assessment of left ventricular ejection fraction by either echocardiography or multigated acquisition scan; and (2) electrophysiological measurement of QT/QTc duration, assessed by electrocardiogram, for predicting risk of a potentially fatal arrhythmia called torsades de pointes. While these and other new safety biomarkers have major value in the development of oncology therapeutics, their applications require careful consideration to avoid unintended consequences that could negatively affect (1) the care of patients with advanced malignancy and (2) the advancement of promising new agents.

Keywords: Safety biomarkers, oncology therapeutics, risk management, cardiotoxicity

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Introduction

A safety biomarker is a treatment-emergent finding that substitutes for or translates into a clinically relevant adverse outcome. To further enhance knowledge regarding the safety profile of new oncology therapeutics, safety biomarkers are receiving increasing attention in the clinical development of experimental products. Products designed to treat advanced malignancy frequently receive regulatory approval for marketing before the risks of uncommon and clinically significant adverse effects have been identified and quantified. For the treatment of a population with major unmet medical need, the safety database for an oncology product may include only a few hundred patients[1] when the product is submitted for regulatory approval. When the safety findings are integrated into clinical summaries submitted for registration and initial product labels, the clinical data may not characterize uncommon safety signals for 2 reasons: (1) dosing and follow-up are commonly limited in duration because of progressive malignancy and the need to initiate other treatments or palliative care, and (2) randomization to placebo may not be accepted by investigators, institutional review boards, and patients with advanced malignancy, so the ability to quantify and characterize safety outcomes against background rates in a control population can be limited.

Decision Making in Clinical Development

In the clinical development of oncology products, safety biomarkers are commonly evaluated at baseline and during treatment. In the situation where the biomarker change can be quantified, threshold values are selected to represent changes of concern that influence decision making in the various ways depicted in Figure 1: (1) eligibility for protocol therapy, (2) analysis of treatment-emergent changes, and (3) dosing changes to modify or discontinue treatment. When appropriate, safety biomarkers can also provide evidence of the pathophysiology and for the diagnosis of a treatment-emergent adverse event.

Safety biomarkers may be more useful when changes can be measured by a linear range of results (in contrast to a binary outcome, eg, positive vs negative), enabling quantification and statistical analyses of changes over a spectrum

Biomarker Strategy	Eligibility	Analyses	Dosing
1	Threshold X	Threshold X	Threshold X
2	Threshold X	Threshold Y	Threshold Z
3	Threshold X	Threshold Y	Actual Adverse Event

Figure 1. Safety biomarkers and decision making in oncology clinical studies. During the conduct of clinical studies, safety biomarkers can affect decisions about eligibility, analyses of treatment-emergent changes, and dose modification or discontinuation. Three biomarker strategies are displayed, representing different threshold values (X, Y, or Z) selected to represent changes of concern as they are applied to decision making during the conduct of clinical studies.

of categories. Ranges of categorical findings are conventionally used in reporting most laboratory and clinical safety outcomes from oncology studies. The categorical changes that constitute increasing severity are typically grades 1 through 5, and specific details of each grade are described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v3.0), openly published for use and referenced in oncology protocols conducted by the NCI, academic centers, and the pharmaceutical industry.[2] Safety biomarkers are also valuable for studies designed to evaluate safety in new indications and populations (eg, pediatric) and for patient management outside of clinical trials after marketing authorization. Safety biomarkers are often applied to a new product based on experience with one clinical product without reevaluation for clinical utility in the new treatment setting, a practice that is usually acceptable because of the paramount concern for patient safety in clinical trials.

Safety biomarkers can enable the advancement of products with preclinical or clinical safety liabilities, both evidence based and hypothetical. While the definition of each severity grade is often determined by a single test, some severity grades are defined as a composite of multiple findings. For example, the CTCAE v3.0 criterion for defining severe (grade 3) cardiac ischemia requires a combined laboratory and clinical event, for instance, (1) "symptomatic" and (2) "testing consistent with ischemia." In contrast, a single laboratory value in troponin I, a biomarker closely linked to myocardial damage, can determine grade 3 changes without corresponding symptoms.

With the increasing applications of new safety biomarkers in clinical studies, consideration must be given to possible unintended consequences, which can take several forms: (1) restricted access to promising treatments; (2) delays in study completion; and (3) limitations to dose delivery, escalation, and the determination of the maximal tolerated dose. Unlike other products' early clinical studies, which are conducted in specialized phase 1 units enrolling normal healthy volunteers, many early clinical studies of oncology products are conducted with patients at clinical cancer centers; thus, unintended consequences can include a cascade of costs and burdens to clinical resources that could otherwise be used to serve the needs of patients with advanced malignancy. Similarly, caregivers can become distracted, turning attention from proper risk assessment and mitigation of adverse clinical outcomes.

The use of uniform thresholds to describe changes of concern for all protocol applications can simplify study conduct and subsequent data collection. For example, the International Conference on Harmonization (ICH) E14 guidance document includes examples of QT/QTc changes of concern often used to manage risk of drug-induced QT/QTc prolongation.[3] The same document includes guidance for risk mitigation in a dedicated clinical protocol designed to evaluate QT/QTc prolongation, so that (1) subjects with baseline QT/QTc exceeding the level of concern (eg, corrected QT/QTc exceeding 450 msec) would not receive treatment; and (2) subjects who develop treatment-emergent QT/QTc prolongation, defined by the same categorical changes of concern (absolute value of 450 msec or prolongation of 60 msec), would have dosing modified or stopped. This guidance for risk mitigation may be generally appropriate when the safety biomarker closely predicts an adverse clinical outcome; in contrast, different thresholds could be used for decision making among the different applications (Figure 1).

Another approach could apply safety biomarkers with thresholds for eligibility and determination of significant treatment-emergent changes of concern, irrespective of biomarker test results, so that only an overt clinical adverse event would determine dose modification or treatment termination (Figure 1). This latter approach would be appropriate in the following circumstances: (1) if the relationship between change in safety biomarker and clinical outcome is not clearly established for the enrolled population; or (2) if treatment modification imposes risks (real or hypothetical) that counterbalance the presumed risk of adverse outcome, reflected by the safety biomarker. In this situation, the biomarker result does not need to be available in real time to enable decisions about treatment for individual patients, although retrospective data analyses could support risk evaluation and dose modification rules for patients treated in later studies.

Separate thresholds for decision making have already been employed in oncology protocol designs. Significant neutropenia may be a commonly measured safety end point for many drugs with nonspecific cytotoxicity; however, an asymptomatic, transient finding of even severe (grade 3) neutropenia would not necessarily drive dose modification or the determination of maximal tolerated dose, especially

when the systemic exposure producing myelotoxicity overlaps with the projected efficacious plasma concentration (C_{eff}). For example, the US label for docetaxel recommends that treatment not be initiated in patients with neutrophil counts <1500 cells/mm^3 (CTCAE grade 2); however, decisions about docetaxel dose modification because of neutropenia typically require reductions to <500 cells/mm^3 (CTCAE grade 4) for more than 1 week and/or clinically evident febrile neutropenia. In several clinical settings that employ cyclic administration of docetaxel or other myelotoxic agents, risks of major clinical consequences caused by neutropenia or stomatitis can be mitigated by use of growth factors such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or palifermin without necessarily reducing the dose of chemotherapy to exposures that may be subtherapeutic.

To further illustrate these concepts, this review will evaluate 2 cardiac safety biomarkers that increasingly affect decision making in oncology clinical studies and patient management. Relevant to the development of a diverse group of oncology drugs and monoclonal antibodies, these biomarkers include (1) assessment of left ventricular ejection fraction (LVEF) by either echocardiography (echo) or multigated acquisition scan (MUGA); and (2) the electrophysiological measurement of QT/QTC duration by electrocardiogram (ECG) for predicting risk of a potentially fatal arrhythmia called torsades de pointes.

LVEF

The evaluation of left ventricular function has typically been measured by serial testing with echo or MUGA to determine LVEF. It has been well documented that echo or MUGA performed serially can detect declines in LVEF and predict risk of clinical cardiomyopathy and congestive heart failure (CHF) after cumulative exposure to anthracyclines, the best studied of cancer therapies associated with cardiotoxicity. Anthracycline cardiotoxicity is a cumulative, dose-related phenomenon[4] in which the risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m^2. The experience with anthracycline cardiotoxicity proved that the early detection and treatment of cardiotoxicity could significantly reduce the development of clinical manifestations, that is, overt CHF and death.[5]

During and after treatment with anthracyclines for solid tumors or leukemia, echo or MUGA changes that suggest declines in left ventricular function are relatively frequent. Anthracyline-related LVEF declines can often be progressive, coupled with overt clinical signs of CHF. Current monitoring guidelines call for a baseline evaluation of LVEF with subsequent evaluations at a cumulative dose of doxorubicin of at least 400 mg/m^2 and periodically thereafter during the course of therapy. In adults, thresholds commonly employed to indicate significant decline in LVEF include (1) absolute LVEF <50% (Grade 2 by CTCAE v3.0[2]), and (2) 20% decrease from baseline irrespective of the final value (Grade 2 by CTCAE v2.0[2]). For agents that are unrelated to anthracyclines and that have no established risk of left ventricular dysfunction after cumulative dosing, a composite threshold has been employed, such as a 10% to 20% decrease, coupled with a decrease to a value below the lower limit of normal.[6] Categories of left ventricular systolic dysfunction, such as those used in CTCAE v3.0, are used to predict impending clinical morbidity, and severe (grade 3-4) changes are thus used to modify the dose regimen or to permanently discontinue treatment of individual patients receiving anthracyclines.

If changes in the safety biomarker are frequent and correspond to adverse clinical outcomes, then a significant change in the safety biomarker can be used to predict the event of interest, especially when there is confidence in the test result and its direct relationship to the pathophysiology of the adverse clinical event (Figure 2). In this situation, a negative result (eg, no significant changes in the safety biomarker) is likely to be informative. Thus, lack of treatment-emergent changes measured by serial MUGA/echo can be viewed with confidence to support decisions about patient management, such as anthracycline redosing. Moreover, the lack of

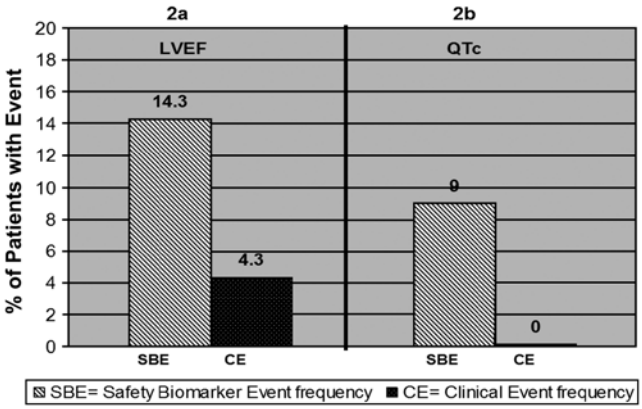

Figure 2. (A) Reported frequencies of abnormal left ventricular function represented by MUGA/echo and clinically evident congestive heart failure.[7] The safety biomarker events are frequent and correlate with frequent clinical events. In such a circumstance, safety biomarker strategies in clinical studies often apply the same thresholds for eligibility, analyses, and dosing. (B) Reported frequencies of prolonged QT/QTc and associated arrhythmia.[8] The safety biomarker events are frequent, but clinical events are rare. In this circumstance, safety biomarker strategies can reasonably apply different thresholds for eligibility, analyses, and dosing. MUGA indicates multigated acquisition scan; echo, echocardiography; QT/QTc, heart rate corrected QT; LVEF, left ventricular ejection fraction; SBE, safety biomarker event frequency; CE, clinical event frequency.

significant treatment-emergent changes of serial MUGA/echo may help to support or refute the diagnosis in a patient experiencing symptoms that mimic cardiac dysfunction such as fatigue or edema, observed in patients receiving some single- or multitargeted tyrosine kinase inhibitors. However, if changes in the safety biomarker are frequent, with poor or undefined specificity to predict the adverse clinical outcome, then the categorical changes described in CTCAE v3.0 may be less informative, and so more customized decision making may be appropriate. For example, declines in LVEF measured by MUGA/echo may be transient and not reliably predict such progressive organ damage, a phenomenon observed after treatment with some new targeted agents.[9] In this situation, MUGA or echo changes could influence decision making using different thresholds in the major protocol applications (Figure 1), especially if there is evidence for control of the malignancy. For example, dosing of a promising tyrosine kinase inhibitor or other targeted agent could conceivably be reinitiated at the same dose after a treatment holiday and additional monitoring for laboratory and clinical evidence of cardiac dysfunction.

When trastuzumab-related cardiotoxicity was initially identified, the oncology investigator community was generally quick to apply risk management strategies to this new product that targeted erbB2. Emerging data from cardiac monitorin g of trastuzumab clinical programs continue to be analyzed; from the pathophysiologic and clinical perspectives, several aspects of trastuzumab-associated cardiotoxicity have been identified. For instance, the incidence and severity of cardiac dysfunction is particularly high in patients who receive trastuzumab in combination with anthracyclines and cyclophosphamide. In some patients, cardiac toxicity develops very early, suggesting the development of an acute inflammatory reaction perhaps resembling acute myocarditis. The clinical course after discontinuation of treatment has not been fully described; however, there have been patients who appear to tolerate continued therapy with trastuzumab after documented declines in LVEF.[9] Current studies of trastuzumab for a variety of breast cancer populations will further characterize the risk of left ventricular dysfunction from such treatment in addition to the value of serial cardiac monitoring by echo or MUGA as a predictor of clinically significant cardiotoxicity. Irrespective of negative or marginal preclinical cardiac findings in nonhuman species, development programs for other agents that target erbB2 have also employed serial testing of left ventricular function, although the performance characteristics and predictive accuracy have not been well defined.[10] Because of issues of reproducibility of results, inconvenience, and cost for serial echo or MUGA, serum cardiac safety biomarkers, such as B-type natriuretic peptide (BNP) and troponin, are also being explored. Early explorative studies of these serum biomarkers have revealed, however, that troponin elevations in at least some subsets of cancer patients may be confounded.[11] Given the unknown predictive accuracy of troponin elevations in patients with advanced malignancy, patient management decisions should be made cautiously when based on only a single elevated serum troponin that reaches some predefined level of concern that has been derived from experience in other populations.

QT/QTc Interval Data

The recent regulatory guidance ICH E14 has spawned growing interest in characterizing the QT/QTc prolonging effects of drugs early in development. For most therapeutic areas, the "thorough QT study" described in ICH E14 establishes the QT/QTc effect, based on established thresholds considered acceptable to support expanded clinical uses and marketing authorization. One challenge for oncology drug development is that an acceptable QT/QTc effect is not easily defined, given the fact that the likelihood of death from progressive malignancy is often 100%, whereas the likelihood of clinical morbidity due to arrhythmia (torsades de pointes) is probably small, even if not characterized precisely. Thus, risk and benefit should be considered when designing clinical protocols and selecting strategies (Figure 1) for the application of safety biomarkers, including decision making based on QT/QTc prolongation. To support rational QT/QTc evaluations in oncology studies, more clinical experience and research are needed so that major decision points in the conduct of clinical studies and patient management, including eligibility, analysis, and dose modification rules, can be designed.

Eligibility and Baseline QT/QTc

Increasingly (and consistent with ICH E14), patients with prolonged QT/QTc or other ECG abnormalities observed at screening are being excluded from clinical trials.[12] However, some studies suggest that cancer patients can exhibit high frequencies (exceeding 30%) of abnormalities in their screening ECG assessments.[13] Similarly, one survey reported that over 10% of cancer patients screened for phase 1 protocols have a prolonged QT/QTc.[14] The epidemiology and baseline cardiac characteristics of cancer patients should be better understood, so that appropriate risk management (eg, restrictions to eligibility) can be carefully determined. Maximizing the number of patients participating in cancer clinical trials while still ensuring safety remains a high priority in oncology. To minimize the number of patients excluded at screening and thus preserve the opportunity to receive promising new agents for treatment of a life-threatening malignancy, protocols should include strategies to enable enrollment after repeat ECG demonstrates an acceptable QT/QTc value, perhaps following modification

of correctable factors (electrolyte abnormalities) or discontinuation of nonessential concomitant medications.

Analysis of QT/QTc Changes of Concern

The Bazett and the Fridericia formulas are commonly used for correction of the QT/QTc interval for heart rate with the choice typically based on characteristics of the compiled data set. Limitations or advantages of the common correction formulas have been described; for example, Bazett's formula overcorrects the QT/QTc interval at heart rates ≥60 bpm.[15] In at least one recent phase 1 oncology study, calculation of QT/QTc by both the Bazett formula and the Fridericia formula resulted in a mean difference of 30.8 msec versus 17.5 msec, respectively, compared with the baseline QT/QTc.[16] Collection of heart rate, uncorrected QT/QTc, and RR interval data should be encouraged in trials where QT/QTc evaluation is intended, so that the more appropriate formula can be used in supplemental analyses.

Table 1. Severity Grading of QTc Prolongation by CTCAE v3*

Grade	CTCAE v3.0
1 = mild	QTc >0.45-0.47 seconds
2 = moderate	QTc >0.47-0.50 seconds; ≥0.06 seconds above baseline
3 = severe	QTc >0.50 seconds
4 = life-threatening	QTc >0.50 seconds; life-threatening signs or symptoms (eg, arrhythmia associated with CHF, hypotension, shock, syncope); torsades de pointes

*According to CTCAE v3.0, a severe (grade 3) Δ QTc prolongation would require a value exceeding 0.50 seconds (500 msec). Treatment-related events of at least grade 3 severity are commonly used for decisions about eligibility, analysis, or dose modification in oncology studies. This definition differs from the level of concern that would influence decisions in other situations, such as a prolongation of Δ QTc >0.06 seconds. QTc indicates heart rate corrected QT; CTCAE, Common Terminology Criteria for Adverse Events; CHF, congestive heart failure.

Dose Modification, Retreatment, and Discontinuation

As discussed above, the use of uniform thresholds to describe changes of concern for all protocol applications can simplify study conduct and subsequent data collection. The ICH E14 guidance provides specific criteria for QT/QTc changes of concern, and these thresholds are increasingly used within the design of protocols used across therapeutic areas, including oncology. The ICH E14 document includes guidance for risk management in a clinical study designed to evaluate QT/QTc prolongation, so that (1) subjects with baseline QT/QTc exceeding the level of concern (eg, corrected QT/QTc >450 msec) would be restricted from treatment; and (2) subjects who develop treatment-emergent QT/QTc prolongation, defined by the same categorical changes of concern (absolute value of 450 msec or prolongation of 60 msec relative to individual baseline), would have dosing modified or stopped.

In a recent publication reporting results of a phase 1 cancer study, Holden et al[8] highlight some inherent challenges in comprehensive evaluation and risk management of QT/QTc prolongation in clinical studies of anticancer agents. While rigorous assessment of treatment-related QT/QTc prolongation was not the primary objective of their phase 1 study, QT/QTc prolongation figured prominently in the reported safety profile and was one of the components determining the maximum tolerated dose. In this study, adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), which have been recently updated to version 3 (Table 1). According to CTCAE v3.0, a severe (grade 3) QT/QTc prolongation would require a value exceeding 0.50 seconds (500 msec). Treatment-related events of at least grade 3 severity are commonly used for decisions about eligibility, analysis, or dosing in oncology studies.

In the Holden et al study, decisions based on QT/QTc prolongation were influenced by more stringent criteria and included rules to hold or reduce the dose of cancer treatment based on asymptomatic QT/QTc prolongation exceeding 60 msec. QT/QTc changes exceeding 60 msec can be observed as a diurnal variation even in healthy volunteers.[17] This criterion for dose modification may be sensitive, but its specificity for predicting clinical consequences has not been well established in oncology treatment settings. Indeed, asymptomatic QT/QTc prolongation was observed across multiple doses, findings that appeared contrary to an exposure-response relationship, and none of the patients were observed to have signs or symptoms of torsades de pointes (Figure 2B).

Two patients who initially received doses ≤300 mg were able to continue treatment at a 50% dose after resolution of QT/QTc prolongation, but both patients later discontinued treatment because of progression of malignancy. Based on pharmacokinetic results analyzed at the completion of the study, only doses ≥300 mg provided plasma levels corresponding to target efficacious exposures (C_{eff}). Therefore, dose reduction for these 2 patients, based on only the asymptomatic QT/QTc prolongation, may have had the unintended consequence of providing subtherapeutic exposures of the experimental treatment.

These results highlight considerations for decision making that are based on safety biomarkers evaluated in oncology studies. The QT/QTc interval is a surrogate safety biomarker for the prediction of torsades de pointes. The relationship is not perfect, however, because the risk of torsades de pointes

may not be a linear function of the QT/QTc interval or a function of the magnitude of the QT/QTc interval prolongation. To preserve the opportunity to receive bioactive doses of agents intended to treat advanced malignancy, decisions about dose modification should be carefully considered. If severe QT/QTc prolongation (grade 3 in CTCAE v3.0) triggers interruption of treatment with an experimental anticancer agent, resumption of treatment employing the same dose could be considered. Retreatment in such a case could be coupled with appropriate ECG monitoring and modification of other factors that can influence QT/QTc. These considerations support applications of QT/QTc measurements as a safety biomarker following strategies that would not modify doses (or contribute to determination of dose-limiting toxicity) based on a single definition for QT/QTc prolongation of concern (Figure 1).

In QT/QTc evaluation during the development of oncology agents, alternative strategies for the definition of changes of concern should be considered, as should impact on dosing. Such alternative approaches should ensure (1) an acceptable safety profile during early and full development, (2) regulatory approval, and (3) adequate labeling and guidance for risk management postapproval.

Conclusions

In the conduct of clinical studies of anticancer agents administered to patients with advanced malignancy, safety biomarker results are playing an increasingly important role. Safety biomarkers may be appropriately used for decision making by the application of uniform criteria, especially in situations where there is a degree of correlation between biomarker changes and corresponding clinical outcomes. A recent example includes MUGA or echo to measure categorical changes in LVEF after exposure to anthracyclines. In contrast, safety biomarkers can be considered exploratory within the design of oncology protocols until clinically relevant outcomes are available.[18] In this latter situation, the impact of safety biomarkers on decision-making criteria may differ in various applications, including eligibility, dose modification, treatment discontinuation, or the definition of dose-limiting toxicity. A recent example includes the evaluation of QT/QTc prolongation during treatment with several drugs that can alter cardiac repolarization. While new safety biomarkers have major value, their applications require careful consideration to avoid unintended consequences that could negatively affect patient care and the development of promising new oncology therapeutics.

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