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Major **Cardiotoxicity** Biomarkers During

Oncology Development

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Cardiotoxicity is now recognized as a common adverse effect of many anti-neoplastic agents.

Targeted anti-tumor therapies and cytotoxic, chemotherapeutic agents have an effect on both the cardiovascular system and the tumor. Consequently, many patients who have benefited from effective chemotherapy now face increased risks of morbidity and mortality from acute and delayed toxic effects of chemotherapeutic agents. According to data from multiple sources, the mortality rate of chemotherapeutic agents due to cardiac events may be as high as 8.2%. This mortality rate increases with cumulative and combination therapies (e.g. chemotherapy and radiation). The risk of myocardial damage from drugs is increased in cancer patients because many, particularly the elderly, have underlying cardiovascular disease. Treatment of cancer now involves administration of complex combinations of chemotherapeutic agents and combination therapy often amplifies cardiotoxicity. Radiation therapy, administered before, during, or after chemotherapy also escalates the risk of myocardial damage.

In the development of new therapeutic entities to treat cancer it is critical to identify those agents with the potential for inducing cardiac dysfunction in subjects participating in clinical trials. **Table 1** is a partial list of chemotherapeutic agents with associated cardiac toxicity.

Doxorubicin is one of the most extensively studied anti-cancer agents and is an example of a drug that produces a wide spectrum of acute and delayed adverse effects on the myocardium. Acute toxicity consists primarily of sinus tachycardia and S-T segment and T-wave abnormalities. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported.

Delayed cardiomyopathy is manifested by a reduction in left ventricular ejection fraction and/or signs and symptoms of congestive heart failure. Other manifestations of cardiac toxicity induced by anti-tumor agents are ischemia, myocarditis, and arrhythmia. A particularly malignant form of ventricular arrhythmia, Torsades de Pointes, associated with a prolonged QT interval, is of increasing concern with anti-tumor agents in development. Therefore, in the clinical investigation of new anti-cancer agents it is important to employ a wide spectrum of modalities to identify all types of cardiac toxicity.

Table 1: Chemotherapeutic Agents and Associated Cardiotoxicity

Chemotherapeutic Agent	Associated Cardiotoxicity
Anthracyclines/anthraquinolones	
Doxorubicin	Left ventricular dysfunction, congestive heart failure
Mitoxantrone	Myocarditis and arrhythmia
Alkylating agents	
Cisplatin	Ischemia, hypertension, congestive heart failure
Cyclophosphamide	Pericarditis, myocarditis, congestive heart failure
Antimetabolites	
Capecitabine	Ischemia
Cytarabine	Pericarditis, congestive heart failure
Fluorourcil	Ischemia
Antimicrotubular agents	
Paclitaxel	Sinus bradycardia, AV block, ventricular tachycardia, hypotension, congestive heart failure, ischemia
Vinca alkaloids	Ischemia
Biological agents	
Rituximab	Hypotension, angioedema, arrhythmias
Trastuzumab	Left ventricular dysfunction, congestive heart failure
Interferon	Hypotension, ischemia, left ventricular dysfunction
Miscellaneous agents	
Arsenic trioxide	QT prolongation
Imatinib	Pericardial effusion, congestive heart failure

Table 2: Biomarkers of Cardiac Toxicity	
Biomarker	**Type of Cardiotoxicity Detected**
Echocardiography	Left ventricular systolic and diastolic dysfunction, pericardial disease, valvular heart disease
Standard 12-Lead Electrocardiography	Rhythm disturbances, conduction abnormalities or blocks, myocardial hypertrophy, ischemia, prolongation of QT/QTc interval
Multi-Gated Acquisition Scan (MUGA)	Systolic and diastolic dysfunction
Troponin I and T	Cardiac injury, myocardial infarction
B-Natriuretic peptide	Cardiac injury, early congestive heart failure

Biomarkers of Cardiac Toxicity

Methods employed to detect cardiac toxicity are echocardiography, MUGA scanning, electrocardiography, and chemical markers of cardiac damage. Cardiac biopsy is also an important tool for detecting cardiac injury but is not practical for routine use in clinical trials. **Table 2** is a list of biomarkers and the types of cardiac toxicity they identify. For the purpose of this discussion the focus will be on echocardiography, MUGA scans, and electrocardiography.

Two Dimensional & Doppler Echocardiography

Echocardiography is the most commonly used non-invasive diagnostic imaging method for real time assessment of heart structure, function, and hemodynamics. Because of its availability, diagnostic advantages, and relatively low cost, echocardiography is rapidly becoming the imaging technique of choice in clinical research. Echocardiography can be readily incorporated into a clinical trial as a marker of cardiac safety and as a measurement of the therapeutic effects of drugs and devices being evaluated for regulatory approval.

Fractional shortening and left ventricular ejection fraction are the two most commonly used echocardiographic indices of left ventricular function. Impairment of these indices is an early sign of left ventricular dysfunction that can lead to irreversible and potentially fatal congestive heart failure. Close monitoring with echocardiography detects early changes that signal a requirement for dose adjustments or discontinuation of treatment. Treatment with an anti-tumor agent is usually discontinued if ejection fraction is decreased by 10 to 15% or to an absolute value of 40% or less.

Several studies have suggested that diastolic dysfunction is an early sign of anthracycline -induced cardiac dysfunction.[1-4] Diastolic dysfunction is the most common early sign of heart failure in patients with normal left ventricular ejection fraction. Comprehensive two-dimensional and Doppler echocardiography can detect abnormal myocardial relaxation, and increased filling pressure in the setting of normal and preserved left ventricular ejection fraction. Therefore, diastolic heart failure should always be considered when left ventricular ejection fraction is normal when determined by two-dimensional echocardiography. Echocardiographic examination along with careful cardiovascular management can not only prevent adverse cardiac events from anti-neoplastic agents but also used to make the appropriate choice of agents for high-risk patients.

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Multi-gated Acquisition Scans

The multiple-gated acquisition (MUGA) scan, also called a cardiac blood pool study, is a widely used technique for estimating cardiac function. The procedure involves administration of a radioactive tracer and requires electrocardiographic gating and an acquisition time of several minutes during which data are accumulated in a computer memory bank. Analysis of the data can provide an estimation of ejection fraction, an evaluation of cardiac wall motion, and an assessment of diastolic function. A MUGA scan may be done while the patient is at rest and again during exercise stress. Because of long acquisition time and required gating, the technique may not be effective in subjects who cannot remain still or who have rhythm disturbances. There is also limited ability to view all structures of the heart with MUGA scans.

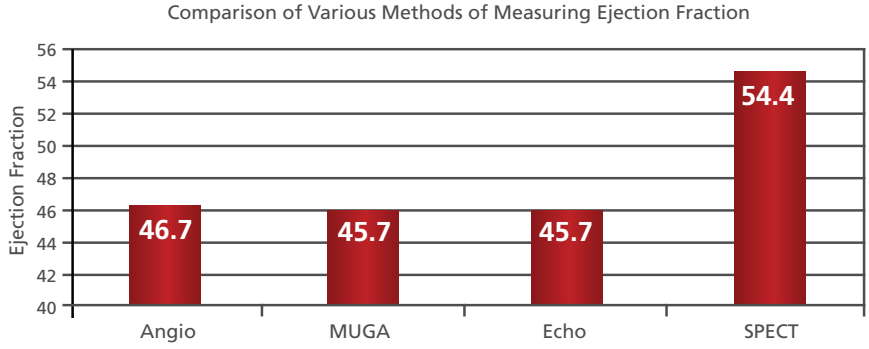
Accurate estimation of left ventricular ejection fraction (LVEF) is critically important in the treatment of patients who receive chemotherapy. A retrospective study of data from 5,558 patients obtained between 1995 and 2004 compared left ventricular ejection fractions determined by invasive angiography, echocardiography, MUGA, and single-photon emission computed tomography (SPECT).[5] The results **(Figure 1)** show a very close positive correlation of the results obtained by echocardiography and MUGA with the data obtained by angiography.

12-Lead Electrocardiography

The standard 12-lead electrocardiogram, which measures and records electrical activity of the heart from 12 points of view, is also easily incorporated into clinical research studies and, similar to echocardiography, it is widely available, safe, non-invasive, portable, low cost, and can be done repeatedly. It is particularly useful for detecting rhythm disturbances, conduction abnormalities or blocks, myocardial hypertrophy, ischemia, and metabolic disturbances. Of increasing importance in drug development is the detection of QT prolongation which may lead to a particularly malignant arrhythmia known as Torsades de Pointes, a potentially fatal form of ventricular arrhythmia.

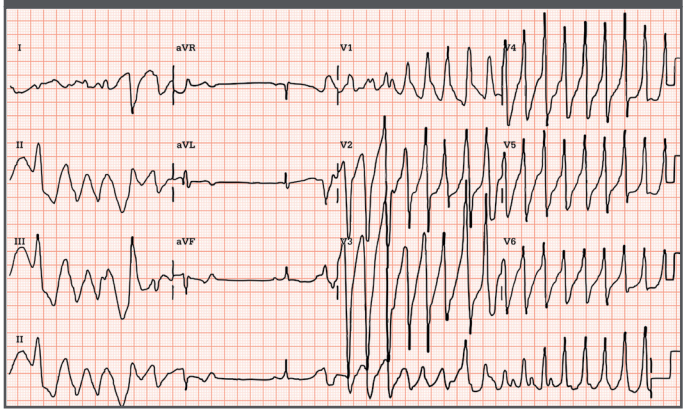
The QT interval is the time between initiation of ventricular depolarization and completion of ventricular repolarization. This interval of approximately one half second varies with hear rate, autonomic tone, age, gender, and time of day. Evaluation of QT prolongation during drug development is now an integral part of pre-marketing safety assessment and the ICH has issued guideline E14 that specifies the protocol to be followed in conducting a Thorough QT (TQT) Study for new drugs. A TQT study measures mean change in QT interval from baseline at selected post-dose time points compared to identical time-matched intervals in a placebo group.

Figure 1: Bar diagram clearly depicting overestimation of ejection fraction by SPECT



Mean LVEF obtained by all four methods yielded a cluster of two values from MUGA and ECHO of 45.7 and 45.7, respectively, significantly below the angiographic average of 46.17 ($p<0.001$), while SPECT was significantly higher than all three at 54.4 ($p<0.001$).

Figure 2: 12-Lead ECG of Torsades de Pointes showing a characteristic long-short ventricular cycle length as the initiating sequence



A mean maximal prolongation of the QT interval of more than five milliseconds is considered to represent an elevated risk of Torsades de Pointes. **(Figure 2).**

For ethical and technical reasons the ICH guideline cannot be applied to the evaluation of most anti-tumor agents because the guideline specifies using therapeutic and supra-therapeutic doses of the test compound and the inclusion of a placebo and active control group. Patients with advanced malignancies cannot sustain a placebo wash-out period or prolonged dosing with a placebo. Therefore, alternative strategies need to be developed to detect drug-induced QT prolongation, and regulatory agencies have accepted departures from the E14 guideline when a TQT study cannot be performed.

An example of an alternative approach to evaluation of QT prolongation is reported in a study by Piekarz et al. [6] The study was an open-label, uncontrolled assessment of the efficacy and safety of depsipeptide in patients with relapsed or refractory T-cell lymphoma. The study was designed in part to determine the effect of depsipeptide on QT interval. Patients were required to have a corrected QTc interval of 500 msec or less to be eligible rather than 450 msec as specified in the ICH guideline. Effects on QTc were assessed as change from baseline.

Mean increase in QTc from baseline was 14.4 msec following treatment. Before treatment three patients had ECGs with QTc >450 msec. After initiation of treatment QTc values > 450 msec were detected in 163 ECGs from 28 patients, > 480 msec in 20 ECGs from 10 patients, and >500 msec in 5 ECGs from four patients. The study supports the employment of practical alternative strategies for cardiac risk assessment. Because the study was an open-label, uncontrolled trial all ECGs were read by one cardiologist under blinded conditions.

Role of the Cardiac Core Laboratory:

The optimal situation is to have biomarker data analyzed and interpreted by skilled analysts at an independent central laboratory. This is particularly important if the data are to be used to support an application for approval of a new chemotherapeutic agent. The use of a certified central laboratory ensures compliance with established guidelines, reduces observer variability, and ensures unbiased interpretation of results.

A cardiac core laboratory, such as BioTelemetry Research, that is highly skilled in the full range of testing modalities adds value during strategic planning and study conduct stages. In the planning phase, core lab experts help to determine which testing modalities will generate the most informative data, in the most efficient sequence. Experienced cardiac safety scientists may also help to design protocols that achieve regulatory expectations for cardiac safety while balancing the complex ethical and logistical issues associated with testing cytotoxic agents.

Most importantly, qualified core labs are able to maximize the value of study results by minimizing data variability. Key factors in establishing accuracy and consistency are well-designed protocols, comprehensive site training, identical modern equipment at every site, state-of-the-art analytical and data management systems, standardized procedures, expert analysts such as board certified cardiologists, and rapid alert reporting.

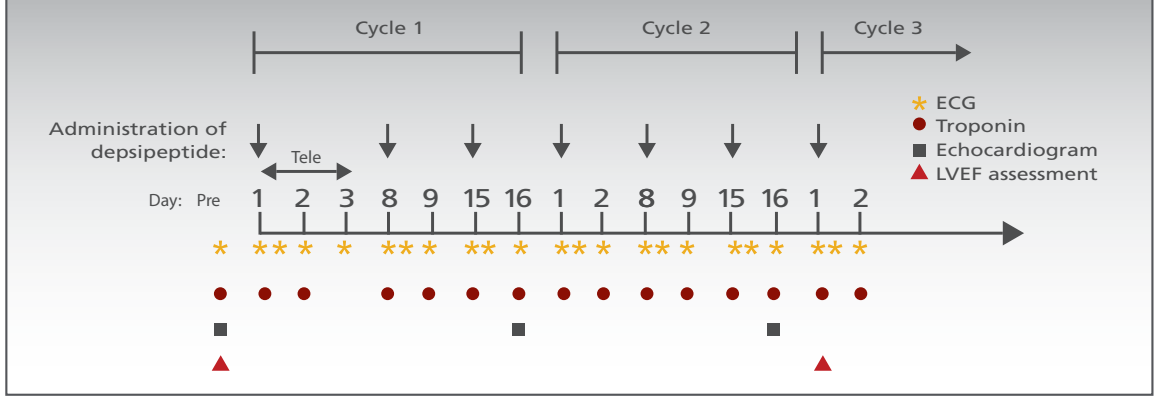
Conclusions:

Cardiotoxicity has become one of the most important complications of cancer chemotherapy, therefore, assessment of cardiac function should be part of every Phase I through Phase III clinical trial of anti-tumor agents in development. Safety biomarkers are playing an increasingly important role in development of chemotherapeutic agents. They are used for determination of patient eligibility, identification of dose-limiting toxicity and making adjustments in dose, based on data obtained from echocardiography, MUGA scans, electrocardiograms and chemical markers of cardiac damage. An excellent example of a comprehensive evaluation of cardiac function with the use of biomarkers in a clinical trial is illustrated in the already cited study by Piekarz et al. 6 In their Phase II study of depsipeptide Pierkarz and coworkers employed a wide spectrum of biomarkers to assess cardiac function in patients with T-cell lymphoma. The timing and nature of the assessments are illustrated in **Figure 3.**

Standard 12-lead electrocardiograms were recorded at baseline, before treatment started, before infusion of each dose, within one hour of the end of the infusion, and on the day after treatment. Echocardiograms were also recorded at baseline and again on the day after the last day of each treatment cycle. Left ventricular ejection fraction was determined in the pretreatment period, after the second cycle and after every third cycle using MUGA, Doppler echocardiography or magnetic resonance imaging. Cardiac rhythm was monitored with a Holter monitor before administration of the first dose and by telemetry after the first dose until discharge on the third day. Chemical markers of cardiac injury (troponin I and creatine phosphokinase) were determined before each dose and the day after each dose during each treatment cycle.

The employment of biomarkers will vary depending on the design of the study, the characteristics of the agent being investigated, and the patient population. However, they should be employed in every study involving an anti-tumor agent. To maximize the value and efficiency of these studies, a qualified cardiac core lab should be employed.

Figure 3: Study Schema



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About BioTelemetry Research

BioTelemetry Research is a leading cardiac core lab that delivers superior global services, expert scientific consulting and state-of-the-art data and information management. Our centralized services include electrocardiography (ECG), Holter monitoring, echocardiography (ECHO), multi-gated acquisition scan (MUGA), protocol development, expert reporting and statistical analysis. With core lab locations near Washington, DC, South San Francisco, CA, London, UK, and Singapore, BioTelemetry Research's global services include Phase I-IV and Thorough QT trials for Top Ten pharmaceutical organizations, specialty pharmaceutical firms and emerging biotech companies.

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Dr. Voloshko has 22 years of experience in ECG, ECHO and Holter research. She is Vice President of Medical Operations for BioTelemetry Research. Prior to joining BioTelemetry Research, she was Vice President of Cardiovascular Clinical Services at the Ischemia Research and Education Foundation and Gentiae. Previously, Dr. Voloshko served as a research fellow at the University of California San Francisco (UCSF) and Chief of Cardiology at Riga City Hospital in Riga, Latvia, an affiliate of the Latvian Medical University. Board certified in cardiology and internal medicine, Dr. Voloshko received her MD, Magna Cum Laude, at the First St. Petersburg Medical School in Russia.

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Dr. McPhillips has 37 years of experience in the pharmaceutical industry in drug development. He is a Senior Pharmacology Consultant for BioTelemetry Research. Prior to joining BioTelemetry Research, he was Director of Clinical Research at Boehringer Mannheim Pharmaceuticals where he directed clinical development programs in oncology, gastroenterology, cardiovascular, respiratory and osteoporosis therapeutic areas. Previously, Dr. McPhillips was a tenured member of the Department of Pharmacology at West Virginia University School of Medicine. He served a member of the editorial board for the *Journal of Pharmacology and Experimental Therapeutics*. He is board certified in toxicology by the American Board of Toxicology, received a BS in biology from St. Joseph's University in Philadelphia and earned an MS and PhD in pharmacology from Thomas Jefferson University.

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