Cardiac imaging approaches to evaluate drug-induced myocardial dysfunction

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The ability to make informed benefit-risk assessments for potentially cardiotoxic new compounds is of considerable interest and importance at the public health, drug development, and individual patient levels. Cardiac imaging approaches in the evaluation of drug-induced myocardial dysfunction will likely play an increasing role. However, the optimal choice of myocardial imaging modality and the recommended frequency of monitoring are undefined. These decisions are complicated by the array of imaging techniques, which have varying sensitivities, specificities, availabilities, local expertise, safety, and costs, and by the variable time-course of tissue damage, functional myocardial depression, or recovery of function. This White Paper summarizes scientific discussions of members of the Cardiac Safety Research Consortium on the main factors to consider when selecting nonclinical and clinical cardiac function imaging techniques in drug development. We focus on 3 commonly used imaging modalities in the evaluation of cardiac function: echocardiography, magnetic resonance imaging, and radionuclide (nuclear) imaging and highlight areas for future research. (Am Heart J 2012;164:846-55.)

The Cardiac Safety Research Consortium (CSRC) (see www.cardiac-safety.org), developed from the US Food and Drug Administration (FDA) Critical Path Initiative, fosters collaborations among academicians, industry participants, and regulators in the assessment of cardiac and vascular safety of new medical products. This CSRC working group report addresses the use of imaging in the evaluation of drug-induced myocardial toxicity. The optimal choice of imaging modality and frequency of monitoring are complicated by many factors. This White Paper summarizes discussions within the CSRC and focuses on what is known, not known, and controversial regarding nonclinical and clinical cardiac functional assessments (methods, parameters, and magnitudes of concern) that are used in measuring cardiac safety risk. This White Paper is intended to assist pharmaceutical companies, clinicians, and regulatory authorities involved in the development of medical products with the potential for cardiotoxicity. The CSRC views expressed in the article are suggestions and do not represent new regulatory policy.

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Background

This White Paper examines the role of imaging in drug development as a means for detecting drug-induced myocardial dysfunction. We focus on 3 commonly used imaging modalities in the evaluation of cardiac function: echocardiography, magnetic resonance imaging (MRI), and radionuclide (nuclear) imaging. Discussion of other modalities not commonly used today in assessing cardiac function is limited. Discussion of nonimaging biomarkers is beyond the scope of this article, and those who are interested in the use of cardiac troponins as biomarkers

for drug-induced cardiac toxicity are referred to another CSRC White Paper by Newby et al.[1] Furthermore, other cardiovascular adverse effects, including QT interval prolongation, proarrhythmic effects, valvular deterioration, myocardial fibrosis, hypertrophy, systemic hypertension, pulmonary hypertension not secondary to left ventricular (LV) dysfunction, thrombosis, inflammation, atherosclerosis, and ischemic coronary artery disease, are not addressed.

The mechanisms of cardiac toxicity are not completely understood for many drugs. There have been speculations on the mechanisms of cardiotoxicity for a number of drugs or classes of drugs, including cytotoxic and immune-modulating drugs (eg, tyrosine kinase inhibitors) used primarily to treat cancer, antipsychotic drugs, and antifungal drugs.[2-6] Some drugs can cause potentially permanent or irreversible myocardial damage (eg, doxorubicin), whereas others may cause potentially reversible cardiac toxic effects.

Early studies demonstrated that the anthracycline-induced myocyte lesion is a predictable result of cumulative dosing, and imaging tools used to detect LV dysfunction could be used to guide the subsequent dosing of doxorubicin and reduce the potential for further cardiac impairment.[7-16] Decreases in ventricular function resulting from significant and irreversible myocardial damage are both concentration-dependent and cumulative dose-dependent and can be monitored by the proactive use of sensitive imaging methods. Subsequent investigators demonstrated that a variety of imaging modalities are sensitive enough to guide anthracycline dosing, although none of them addresses the appropriate frequency or duration of monitoring required in patients receiving cardiotoxic agents, the threshold for change in LV ejection fraction (LVEF), or the absolute value to be used as a decision point for continuing or discontinuing therapy. More recently, it has become apparent that serial changes in LVEF may not be sensitive enough to detect early myocyte damage; therefore, using other potentially more sensitive imaging modes, such as Doppler echocardiography for evaluating LV relaxation and myocardial strain rate and measuring serial cardiac biomarkers such as cardiac-specific troponins and brain natriuretic peptide (BNP), may provide additional information.[1,17-21]

The optimal choice of the myocardial imaging modality and the recommended frequency of monitoring remain undefined. These decisions are complicated by the array of imaging techniques, which have varying sensitivities, specificities, availabilities, intrasubject and intersubject variability, local expertise, safety, and costs and by the variable mechanisms, time courses, and degrees of drug-induced tissue damage, functional myocardial depression, or potential recovery of function. There is also a limited understanding of the clinical significance of modest changes in LVEF and other measures of cardiac function as well as a lack of comparative studies evaluating the effectiveness of cardiac imaging modalities in clinical development and clinical settings. This article, therefore, summarizes CSRC views on the main factors to consider when selecting nonclinical and clinical cardiac function imaging techniques in drug development and underscores the need for head-to-head prospective trials comparing the various imaging modalities available to assess myocardial dysfunction.

Nonclinical considerations

Cardiac imaging to assess changes in cardiac function is not routinely included in the nonclinical assessment of cardiac toxicity. In 2011, Leishman et al reviewed the best practices for nonclinical cardiovascular assessments (invasive methods interrogating acute hemodynamic changes during typically short duration safety pharmacology studies).[22] Nonetheless, in repeat-dose nonclinical cardiovascular safety studies, cardiac imaging can assess cardiac relaxation and contractility (ie, diastolic as well as systolic function) as part of an integrated assessment of structure and function. In particular, focused cardiac imaging studies are useful when applied to drug classes of potential concern (eg, specific kinase inhibitors[23]) to detect chronic or progressive cardiotoxicities, or in longitudinal studies to evaluate the reversibility of the cardiotoxic effects and provide potential mechanistic insights. When nonclinical cardiotoxicity is observed, determining reversibility and potential mitigation is important in risk-benefit assessments and decision making for further advancing the drug into clinical development.

Transthoracic echocardiography remains the foundation for noninvasive assessment of cardiac structure and function and has been used with different classes of compounds.[24-29] Standard 2-dimensional (2D) echocardiograms are relatively insensitive to small changes in cardiac function that could be of interest in early drug discovery. This is particularly true for animals with small hearts and rapid heart rates (eg, rodents). Currently, applications of cardiac imaging in nonclinical drug discovery and development are evolving with investigation of newer approaches including post–contrast MRI in rats,[30] echocardiography with tissue velocity and speckle-tracking based strain analysis in adult mice,[31] pressure overload models using aortic constriction, and stress echocardiography testing in rats.[32] Although such techniques have not yet been widely validated, with further study, their enhanced sensitivity may prove beneficial in predicting and detecting drug-induced cardiac effects.

Nonclinical cardiac imaging can be both a sensitive and specific methodology to measure small changes in cardiac function. In the same way that imaging can be used in nonclinical efficacy studies to either inform nonclinical project decision making or to validate

imaging biomarkers for future clinical studies, nonclinical imaging studies of potential cardiotoxicity can be used either to evaluate the risk of progressing into humans or to validate a safety imaging biomarker for clinical studies. Imaging biomarkers can be coupled with other available biomarkers (eg, cardiac troponins, BNP, or N-terminal prohormone of BNP) to improve the sensitivity and specificity for the detection of cardiac toxicity. In the nonclinical and clinical settings, there is no consensus with respect to threshold values for these biomarkers for evaluating drug-induced cardiotoxicity. What is important in the nonclinical setting is to detect cardiotoxicity signals early and monitor how translatable the signal may be in humans. Determining and enhancing the predictive value of the various imaging modalities is an area of active investigation.

Review of clinical echocardiography, MRI, and radionuclide imaging for the detection of drug-induced cardiotoxicity

Echocardiography

Echocardiography is the most widely applied noninvasive modality that provides data on cardiac structure and function[33] and plays a critical role in the clinical evaluation of the potential therapeutic and cardiotoxic effects of pharmacologic agents in all phases of drug development.[34-37] The current standard for clinical practice and investigation, 2D echocardiography with Doppler flow assessments, can characterize hemodynamics and systolic/diastolic function and can display cardiac structures and measurements of cardiac chamber sizes. Three-dimensional (3D) echocardiography is a modality that offers the potential to enhance assessments of cardiac function, structure, and geometry. The discussion below is based predominantly on 2D echocardiography with Doppler flow assessments, except as noted.

Advantages include the following:

- Nonclinical and clinical standard. Echocardiography is widely used for monitoring ventricular function.[33,34,38]
- Ease of use. Echocardiography is easily performed, widely available, relatively inexpensive, and highly portable. There is no ionizing radiation and no limitation with claustrophobia or with existing metallic implants. Echocardiography provides real-time data without the need for electrocardiographic (ECG) gating and is a preferred method when frequent serial assessments (eg, weekly or every 2 weeks) are needed.
- Contrast agents not required. With echocardiography, contrast agents are generally not required except when image quality is poor. However, their use enhances image quality and reduces variability.
- Comprehensive data collection. Echocardiography provides detailed information on cardiac structure (atrial and ventricular cavity dimensions, areas, volumes, wall thickness, and mass), cardiac function (systolic and diastolic, right ventricular and LV, wall motion, fractional shortening and ejection fraction, global and regional, and preload and afterload), valvular disease (structure, function, and degree of regurgitation or stenosis), vascular structures,[34,39] and hemodynamic data.

Disadvantages include the following:

- Image variability. Sources of variability, especially when comparing follow-up with baseline images and intersubject comparisons, can arise during both image acquisition and image interpretation. During image acquisition, the sources of variability may be attributed to a number of factors, including different skill levels of the sonographer, different machines or imaging modes (eg, fundamental imaging or harmonic imaging, 2D, or 3D), different acoustic windows or imaging planes used, inadequate image quality, and biological variability of the patient (eg, changes in preload or afterload). During image interpretation, the variability may arise from different algorithms used (eg, single-plane or biplane method for LVEF) and interreader variability.[38] Measures to minimize these variabilities include standardized image acquisition protocols, centralized image interpretation, and intensive reader training. Under conditions such as chemotherapy in patients with advanced cancer, marked changes in intravascular volume status, heart rate, or blood pressure might also contribute to increased variability in serial assessments of cardiac function. However, these extracardiac factors can also influence other imaging modalities.
- Image quality. Poor acoustic windows can result in poor visualization of the LV endocardial border, making quantitation of the LVEF difficult or inaccurate. Poor acoustic windows limit image quality in up to 10% of patients, in whom the use of ultrasound contrast agents may be appropriate when at least 2 contiguous segments of the LV endocardial border are not visualized.[40]
- Limitations due to resting conditions. During drug development, echocardiograms are typically obtained while the participant is at rest. This could potentially limit the detection of cardiotoxicity that may only become apparent under stress conditions using exercise or administration of a pharmacologic agent such as dobutamine.

Measures can be taken to mitigate these limitations. Sources of variability can be minimized by using experienced sonographers, standardized image acquisition protocols,[41] limited number of well-trained readers, centralized image readings with standardized methods

for image quantification and analyses, and careful attention to procedural techniques and quality control.

Advances in technology continue to improve the quality and quantity of data achievable through echocardiography. Two-dimensional echocardiography with Doppler imaging has become the most widely used modality in the evaluation of systolic and diastolic LV function. Strain imaging of the LV is a new methodology to evaluate cardiac deformation and function and may detect myocardial injury before reduced systolic ventricular function is evident, as measured by decreased LVEF.[42] Three-dimensional echocardiography eliminates the need for geometric assumptions used in 2D technique and may offer improved precision and reduced variability for assessment of LV volumes and LVEF.[43-45] These techniques and expertise are not as widely available but should be considered in the appropriate clinical setting.

Magnetic resonance imaging

Cardiac MRI is an accurate, reproducible, and well-validated technique for measuring left and right ventricular volumes and mass and is a recognized imaging modality for many cardiovascular applications.[46]

Advantages include the following:

- Image quality. Cardiac MRI produces high-resolution images with soft tissue contrast, without the need for ionizing radiation.
- Precision. Cardiac MRI does not rely on geometrical assumptions to calculate volumes and is, therefore, reliable even in remodeled hearts with complex geometry.[46] Of note, 3D echocardiography also measures similar changes in volume and LVEF to those obtained using MRI, although there may be difficulties in full heart coverage for large hearts and issues with image quality.[47,48]
- Reproducibility. Cardiac MRI provides excellent inter-study reproducibility, resulting in reliable estimates of observed changes and reduced participant numbers in clinical trials.[49] Different methods for obtaining LV volumes and LVEF including 2D echocardiography, radionuclide ventriculography, and cardiac MRI are not interchangeable.[50] Cardiac MRI may be the preferred technique for volume and LVEF estimation in patients with heart failure because of its 3D approach for nonsymmetric ventricles and superior image quality.
- Comprehensive data collection. Cardiac MRI provides comprehensive structural and functional data including LV/right ventricular dimensions, volume, mass, and systolic function. Indeed, cardiac MRI is capable of determining the amount of myocardial fibrosis and/or inflammation.

Disadvantages include the following:

- Expense. Cardiac MRI has a higher cost relative to echocardiography and radionuclide scans.
- Access. Cardiac MRI is not as widely available as echocardiography and is nonportable. In certain regions and countries, high-quality cardiac MRI and clinical expertise in interpretation may not be readily available, increasing the logistical difficulty of organizing large multicenter clinical trials. There is also limited availability in a nonclinical setting.
- Contraindications. Contraindications to cardiac MRI include claustrophobia, metallic implants such as pacemakers, defibrillators, insulin pumps, aneurysm clips, or any other foreign metallic body, and limitation in large body size (eg, body mass index >38 kg/m^2). There is also a requirement for regular cardiac rhythm for ECG-gated image acquisition.
- Nonadherence. There is a risk of nonadherence to undergoing a cardiac MRI due to patient discomfort and screening time.

There are a variety of techniques to measure cardiac function beyond volume measurements when using cardiac MRI.[51-53] Moreover, results from these techniques can be translated between the nonclinical and clinical environments.[54-56]

Radionuclide (nuclear) imaging

Nuclear imaging has long been used for the detection and monitoring of chemotherapy-induced cardiotoxicity.[57,58] Radionuclide angiography techniques, known as gated blood pool scans, multigated acquisition (MUGA), or equilibrium radionuclide angiography, are recognized for monitoring cardiac function and cardiotoxicity.[59-62]

Advantages include the following:

- Reliability. Nuclear imaging has a long and well-established track record of reliable results in monitoring the cardiac effects of chemotherapy, accuracy, and precision of measurements of LV systolic function and reproducibility in the determination of LVEF.
- Well-established standard for monitoring LV function.
- Relatively operator independent.
- Less costly than MRI.

Disadvantages include the following:

- Expensive compared with echocardiography.
- Access. Nuclear imaging is not as readily available as echocardiography. Availability and expertise in specific nuclear imaging modalities vary by center.
- Ionizing radiation exposure. Nuclear imaging requires exposure to ionizing radiation, which can be a limiting factor if repeated studies are required.
- Limited information on anatomical details. Cardiac nuclear imaging lacks the ability to collect information on anatomical details of the heart, such as valvular disease, diastolic function, and hemodynamic

assessments as well as additional information on adjacent structures.
- Requirement for normal sinus rhythm for ECG-gated image acquisition.

Because of the well-established reproducible results, radionuclide angiography has compared favorably with 2D echocardiography for monitoring LV systolic function.[48] However, with the advent of newer echocardiography and MRI techniques, recent studies have used these other modalities for end points of ventricular function either in addition to, or instead of, radionuclide angiography.[63-65] For example, 3D echocardiography has been shown to be a reasonable alternative to MUGA for following ventricular function in subjects undergoing chemotherapeutic treatment for breast cancer.[48] In subjects with severely depressed systolic function, MUGA remains a more reliable imaging modality than 3D echocardiography, possibly due to enhanced visualization of the apex.[66]

With radionuclide angiography, the primary parameter for the detection of cardiotoxic effects remains the LVEF.[62] Radionuclide angiography has excellent interexam precision and reliability for the measurement of LV function and volumes.[67]

Exercise stress radionuclide angiography has proven sensitivity in the detection of cardiotoxicity.[68] However, with exercise, the failure to increase LVEF during radionuclide imaging has low specificity and does not appear to support its use for monitoring purposes.[69] Nuclear indices of diastolic dysfunction, such as decreased peak filling rate, have also been evaluated for their utility in the early diagnosis of cardiotoxicity.[61] However, neither exercise blood pool scanning nor diastolic function assessments are currently part of mainstream nuclear practice. Despite the initial promise of diastolic dysfunction as an earlier marker of cardiac dysfunction than LVEF, studies using radionuclide ventriculography suggest that systolic and diastolic parameters decline in tandem in the early stages of cardiotoxicity.[70,71]

Application of imaging techniques in clinical trials

It is important to monitor cardiac function in the course of clinical trials when evaluating agents with known or suspected cardiotoxicity. The level and frequency of monitoring in a trial may be based on nonclinical signals, known or assumed drug class effects, or prior experience with the drug currently under investigation, as well as factors such as the pharmacokinetic and pharmacodynamic properties of the drug.

Commonly and particularly in oncology trials, LV function is assessed by measuring LVEF at baseline and at multiple intervals during treatment and after completion of drug administration, although the follow-up period often does not exceed 1 year. However, longer follow-up periods with at least semiannual or annual examinations of LV function may be necessary after administration of treatment with drugs known to cause irreversible or delayed heart failure. Largely due to good reproducibility, MUGA scans have historically been a frequently used imaging modality in oncology clinical trials for the assessment of drug cardiotoxicity.[72] However, the use of echocardiography to obtain a more comprehensive assessment of both systolic and diastolic function is also common.

Although detection of a decrease in LVEF can be highly reproducible using various imaging modalities, such a decrease is often a late result of cardiac toxicity, and the progressive loss of functional myocardium can lead to poor cardiac clinical outcomes.[73] Recent data suggest that isovolumetric relaxation time, peak filling rate, and various Doppler and strain imaging measurements may offer more sensitive measures of early cardiac injury than standard echocardiography techniques.[72,74]

In some situations, for patients who may have demonstrated decreases in LVEF but are considered to be appropriate candidates for continuing drug therapy based on clinical response (eg, oncology), more frequent monitoring (such as before each chemotherapy cycle) may be considered. Regardless of which imaging modality is selected, it should be readily available to help treatment decisions and to avoid delaying a potentially lifesaving therapy (eg, anticancer therapy).

Centralized reading of cardiac images is increasingly being used in clinical trials to assess drug cardiotoxicity. The imaging charter, which is a document that provides a comprehensive and detailed description of the clinical trial's imaging methodology, should be standardized across all sites in a study.[41] Point-of-care readings can be used for acute patient management, whereas centralized readings have been recommended for overall study evaluation to ensure consistent data interpretation. In some cases, the expertise of the central readers is essential in the interpretation of state-of-the-art imaging techniques (such as 3D echocardiography and strain assessments) or recognition of a finding that must be communicated to the point of care, when such assessments are essential in risk minimization. This centralized quality control and reading approach can decrease the variability in the interpretation of the images[38] without compromising the timeliness of safety monitoring. In addition, clinical event committees may be used to evaluate the occurrence of protocol-defined cardiac events that occur during the trial and the period of drug administration, along with later follow-up.

Long-term follow-up is important to correlate cardiac imaging results with adverse clinical cardiac outcomes.[42] The need for long-term follow-up, however, must be balanced with the need to bring effective agents to the clinical arena rapidly.[72] Such goals should be coordinated. Comorbidities in high-risk populations and the natural course of the disease may limit the ability to conduct long-

term follow-up in some patient subsets. The same imaging modality should be used throughout the study for each patient, and sponsors should ensure that there is the ability to provide rapid interpretations with minimal reader variability.

How is imaging detection of impaired cardiac function used in clinical trials?

Morbidity and mortality are clearly associated with both progressively lower LVEFs and symptomatic heart failure. In a clinical trial, specific criteria for participant inclusion, exclusion, discontinuation, dose modification, and drug rechallenge are dependent upon the overall benefit-risk profile of the treatment in the context of the disease process. An advantage of a clinical trial setting is that baseline testing can be planned and obtained routinely for later comparison and decision trees can be formulated to guide management decisions. The decision to continue a "cardiotoxic" treatment in an individual (eg, allow continuation of treatment despite a declining LVEF) is dependent upon a benefit-risk assessment for each participant in the study. Inclusion of participants in a trial to treat refractory end-stage metastatic disease would be regarded differently from their inclusion in a program to test a new compound as adjuvant chemotherapy. At this time, there is no uniformly accepted approach to these thresholds of concern or action. Different companies, regulatory agencies, and professional societies have adopted different approaches to this issue. Moreover, this issue is particularly challenging in early drug development where the potential efficacy of the new drug has not yet been estimated. Nonetheless, the general philosophy is that potential risk versus potential benefit varies based on the overall benefit-risk profile, specific patient clinical characteristics, and patient preferences. Judgment is needed both for the individuals in the trial as well as the overall trial's goals in the context of the drug development process.

The concept of a cardiotoxicity threshold, therefore, may be viewed as a balance of the benefits of the drug, tempered by the expected course of the underlying condition, availability of alternative treatment options, and individual patient tolerance of and preference for the specific treatment. Cardiotoxicity may be evaluated in a number of ways, including absolute LVEF percentage point change from baseline, categorical analyses of the proportion of subjects whose LVEF declines below defined thresholds, and other clinically pertinent assessments that might be specific to a compound, condition, or patient population (eg, LV hypertrophy, valvular degeneration, symptomatic heart failure, myocardial fibrosis or calcification, etc). Changes in cardiac function as assessed by imaging must be interpreted in the context of clinical findings and other evidence of cardiotoxicity such as changes in heart rate, blood pressure, ECG changes, and biomarkers such as cardiac troponins, BNP, or C-reactive protein. However, the acceptable threshold for decrease in cardiac function varies considerably based on a number of factors, including patient characteristics such as age, prognosis of disease under treatment, preexisting heart disease, other comorbidities, and concomitant medications.

Adverse reaction classification tools such as the Common Terminology Criteria for Adverse Events (CTCAE) v4 criteria,[75] commonly used in cancer trials, can be helpful in determining the need for dose adjustments or discontinuation at a patient or study level. These tools provide general guidance to suggest levels of severity of injury or dysfunction that may be used to define dose alterations, but the stated ranges ultimately are arbitrary and have to be interpreted for each drug-disease-patient situation. The decision to alter or interrupt drug therapy due to cardiotoxicity may also be guided by other biochemical markers (eg, cardiac troponin, BNP), nonclinical information (eg, reversibility of cardiotoxicity upon drug withdrawal), and drug class effects. The process may be iterative, and greater allowance for more toxicity may be justified under more serious conditions.

Furthermore, it is important to monitor long-term survivors who have been exposed to known cardiotoxic agents on an annual basis (or other appropriate interval for the drug, condition, and patient population), as late effects may not be detected by any available techniques at an earlier stage for several reasons: effects developing after the time of active treatment (sometimes considerably longer), monitoring techniques are not sensitive enough, or the superimposition of confounding comorbidities (ie, ischemic heart disease, diabetes, and hypertension). Currently, the frequency and duration of monitoring in patients receiving cardiotoxic agents are undefined.

Future directions

A variety of therapeutic compounds may have a deleterious effect on myocardial function and structure. These effects can range from subtle findings detected only by serum biomarkers, to changes in cardiac function on imaging, to overt clinical heart failure. They may occur during the course of treatment or become evident many years later. Although the risks of such cardiotoxicity must be weighed against the actual benefits of the drug and tempered by the expected survival with the underlying disease process, further investigation would contribute to the overall understanding of cardiotoxicity and allow the development of best practices for safety surveillance using cardiac imaging. Furthermore, determining which imaging modalities are optimal for detection of cardiotoxicity and how to best use the available modalities would be helpful in designing clinical trials to evaluate preventive or therapeutic strategies.

Despite the limitations of the currently available technologies, it is still reasonable to collect available nonclinical and clinical data on imaging and blood biomarkers, to investigate the correlation between imaging and blood biomarkers, and to determine how this information can be used in predicting clinical safety outcomes. Using this approach, evidence-based guidelines could be developed for imaging and blood biomarker-guided therapy. Drug development clinical trials provide opportunities for prospectively assessing the utility of cardiac imaging modalities to reduce adverse cardiovascular outcomes.

To realize these goals, a number of strategies are suggested here:

- Adequate nonclinical safety evaluation of drug-induced cardiotoxicity including measurement of cardiac function.
- Adequate trial design for the detection of cardiotoxicity including robust safety monitoring of compounds suspected of causing cardiac dysfunction.
- Inclusion of cardiovascular specialists and those with relevant imaging expertise on the investigative team during protocol development, clinical care, and evaluation phases. Although such expertise is particularly valuable early in the study design process, it is also essential to the safe conduct of the trial and correct interpretation of results. In addition, having cardiologists engaged in the clinical trial can assist with earlier detection of potential signs and symptoms of cardiotoxicity and referral for closer monitoring and treatment.
- Standardized image acquisition and analysis protocols in clinical trials designed to assess cardiac function, changes in function and detect cardiac dysfunction for each relevant modality. These methods should be developed based upon existing professional society recommendations modified for clinical research purposes.[34]
- Use of experienced and trained readers for centralized image analysis and quantitation. Such centralized image reading should follow best practices[38,76] including, but not limited to, prospective reproducibility testing. Where there is uncertainty, methodologic research may be needed to define the optimal approach.
- Qualification of key imaging end points for assessing cardiac function and detection of cardiac dysfunction as quantitative biomarkers for use in clinical trials.[77-79]
- Imaging informatics with standardized definitions of critical data elements related to cardiac function, dysfunction, structure, and cardiovascular safety end points that can be used across clinical trials and registries of the same compound preapproval and postapproval. Ideally, a core set of data elements would be defined and used to better understand cardiotoxicity across compounds and across imaging modalities.
- Reaching a consensus definition of cardiotoxicity, including which imaging findings and thresholds are to be used in clinical research to detect cardiac damage.
- Inclusion of standardized imaging data elements in relevant clinical oncology and cardiovascular registries for monitoring the short-term incidence of chemotherapy-induced cardiac dysfunction and the long-term postapproval safety of chemotherapy on the heart. It is also important to assess the incidence of cardiomyopathy in various cancer patient populations not treated with cardiotoxic medications.
- Use of better imaging biomarkers, including exploration of emerging imaging modalities and techniques, to predict clinically meaningful and potentially irreversible versus reversible changes in cardiac function.
- Use of common and complementary nonclinical and clinical methods, imaging modalities, biomarkers, histopathology, and assessments with appropriate models to advance predictive cardiac-related safety science.
- Prospective use of thresholds for clinical decision making for dose escalation, dose reduction, and dose discontinuation in clinical trials (eg, reduction in LVEF by >xx% units to <yy% or >aa% to <bb%) to determine the effect on short- and long-term outcomes. For example, several thresholds could be assessed such as: absolute reduction in LVEF of >10% or >15% units; combination of LVEF reduction >10% or 15% to a threshold <55% or <50%, and others. Currently, there is no consensus as to what threshold should be used, and these thresholds may vary based on comorbidities, benefit-risk assessment, and concomitant medications.
- Inclusion of evaluations of various pharmacologic therapies in nonclinical and clinical studies to determine if these therapies improve the benefit-risk profile.
- Develop evidence-based algorithms in prospective clinical trials for the integrated use of cardiac imaging modalities to maximize utility while minimizing risk, resources, inconvenience to patients, and costs, based on cardiovascular outcomes data.
- Evaluate the utility of using other cardiac imaging modalities (eg, computed tomographic and positron emission tomographic scans) for monitoring cardiotoxicity in clinical trials.
- Advance the use of cardiac imaging modalities to assess additional manifestations of cardiotoxicity, such as hypertrophy (resulting from systemic hypertension or other trophic effects), fibrosis, calcification, cardiac dysfunction from metabolic abnormalities, right heart failure resulting from pulmonary hypertension and other etiologies, and valvular deterioration, in addition to overt cardiac dysfunction as currently evaluated.

Concluding comments

The discussions in this White Paper summarize areas of emerging consensus on the role of cardiac imaging for

monitoring drug-induced cardiotoxicity in clinical development and other areas in which consensus remains elusive and also provide suggestions for additional research to further our knowledge and understanding of this topic. The ability to make informed benefit-risk assessments for potentially cardiotoxic new compounds is of considerable interest and importance at both the public health level (lifecycle drug development and treatment availability) and the individual patient level (clinical care decisions made by patients in conjunction with their personal healthcare provider). Cardiac imaging approaches in the evaluation of drug-induced myocardial dysfunction will likely play an increasing role in drug development and benefit-risk assessments. The CSRC therefore hopes this White Paper will facilitate discussions among all stakeholders that will lead to improved application of use and enhanced utility of cardiac imaging in drug development.

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