



Review

Opportunities to meet clinical cardio-oncology needs with new approaches to non-clinical safety assessment



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ABSTRACT

Marked successes in treating a wide variety of malignancies in both adults and children have raised concerns about the cardiotoxic sequelae of several mainstream and emerging cancer therapies. There is a critical need for the health care community to more quickly and reliably identify the unique treatment-related cardiac risks facing patients with cancer. Meeting these needs will likely involve identifying new biomarkers of early and reversible cardiotoxicity, designing and optimizing dosing and drug selection, and developing oncology drugs that can be administered with protectant therapies to improve safety profiles. Non-clinical studies offer the opportunity to more thoroughly characterize underlying biological mechanisms that might aid in designing and optimizing safer drugs. The Health and Environmental Sciences Institute (HESI), a global, non-profit institute that promotes multi-sector scientific partnerships along with other academic, government, patient-advocacy, and clinical partners, proposes to develop novel collaborations to develop new ways of performing non-clinical safety assessments that will benefit patient quality of life.

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1. Introduction

Traditional approaches to non-clinical safety assessment for new medicines are not often specific to patient phenotypes and clinical treatment regimens. Nowhere is this truer than for oncology drugs, for which poly-pharmacy is the norm, co-morbidities are common, treatments can last from weeks to years, and patients can be of any age. Marked successes in treating a wide variety of malignancies in both adults and children have raised concerns about the cardiotoxic sequelae of several mainstream and emerging cancer therapies. These concerns have prompted a unique partnership among cardiologists and oncologists (e.g., International Cardio-Oncology Society) and related workshops (e.g., NCI/NHLBI workshop “Cancer Treatment-Related Cardiotoxicity: Understanding the Current State of Knowledge and Developing Future Research Priorities,” Bethesda, MD; March 2013) to improve clinical approaches to detecting and managing treatment-related toxicity in patients with cancer [1,2].

Members of the Health and Environmental Sciences Institute's (HESI) Cardiac Safety Technical Committee recently met with members of this community in a satellite roundtable discussion after the International Colloquium on Cardio-Oncology in Rome, Italy. This discussion explored

opportunities for the non-clinical cardiovascular safety community to contribute to this partnership by improving the understanding and management of clinical cardiotoxicity resulting from cancer therapies. Specifically, the attendees identified a critical need for the health care community to more quickly and reliably identify the unique treatment-related cardiac risks facing patients with cancer. Meeting these needs will likely involve identifying new biomarkers of early and reversible cardiotoxicity, designing and optimizing dosing and drug selection, and developing oncology drugs that can be administered with protectant therapies to improve safety profiles.

The Health and Environmental Sciences Institute (HESI) is a global, non-profit institute that promotes multi-sector scientific partnerships between academic, government, clinical, non-governmental organizations, and industry stakeholders to develop and validate new approaches to improve human and environmental health. HESI's Cardiac Safety Committee conducts research and develops best-practices through a series of working groups dedicated to improving the clinical relevance of non-clinical cardiovascular safety assessment. The Committee has ongoing initiatives on pro-arrhythmia prediction, biomarkers of coagulation, induced pluripotent stem-cell-derived cardiomyocytes as in vitro testing platforms, and integrative approaches to drug safety assessment [3].

Non-clinical pharmaceutical safety assessment is a globally regulated process that uses several prescribed in vitro and in vivo assays. These assays are important in assuring safety at all pre-clinical and clinical phases of drug development. Importantly, most standard in vivo non-

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clinical safety evaluation assays involve animal models generally consisting of healthy adult animals. As such, non-clinical databases and evidence are built on evidence from a relatively homogenous set of animal model phenotypes. In vivo assessments of acute drug-induced changes in cardiovascular function are outlined in ICH guidelines (S7a, S7b). These assessments have translated well from animal models to clinical use and have protected patients in Phase I clinical trials from severe and unintended adverse effects [4,5]. Although these studies are generally single-dose studies of instrumented animals where a range of physiologic cardiovascular measures are possible, they tend to be biased toward a focus on ECG measures of pro-arrhythmic risk as the endpoint of primary concern because drugs that prolong the QT interval may induce fatal arrhythmias.

Repeat-dose general toxicity studies are a mainstay for evaluating the more chronic risks associated with new drugs and include both morphologic (e.g. histopathologic) and biochemical endpoints (clinical pathology assessments). Histopathologic analyses can assess drug-induced changes in cardiac structure with much more precision than is possible with clinical endpoints. Alternatively, cardiac troponins and natriuretic peptides are sometimes collected in these animal studies much like they are from patients with cardiovascular disease [6]. Measures of cardiac function in repeat-dose studies are often restricted to non-invasive ECG measures, although the capacity is improving in the measurement of blood pressure with non- or minimally-invasive methods and cardiac contractility with echocardiography [7].

Standard single- or repeat-dose, pre-clinical toxicity studies in animals have for decades provided important assessments of potential safety risks, but new approaches to preventing and monitoring long-term health risks in particularly susceptible patients are needed. Clinically relevant, non-clinical study designs are needed to explore the effect of single or combined treatments in animals with neoplasia, with other co-morbidities, pre-treated with anthracyclines, or receiving additional radiation therapy. New dosing strategies (bolus, repeat-, interrupted-dose) and protective therapies need to be developed. Clinically relevant cardiac function needs to be assessed in repeat-dose studies that can be augmented with high-resolution morphologic assessments (e.g., with light or electron microscopy), transcriptomic endpoints, or even cellular biochemistry [8]. Non-clinical studies also offer the opportunity to more thoroughly characterize underlying biological mechanisms that might aid in designing and optimizing safer drugs.

However, the difficulties designing, conducting, and funding such studies should not be underestimated. Patient phenotypes and genotypes are incredibly variable and not easily replicated in animal models. Therapeutic regimens are likewise variable and are often personalized for an individual patient or tumor type. Substantial efforts and diverse expertise are needed to ensure that the outcomes of such studies are robust and relevant.

To achieve these challenging goals, strong partnerships among stakeholders are needed to develop new ways of performing non-clinical safety assessments. Stakeholders must determine how these studies would support contemporary safety regulations. These studies cannot draw on the considerable experience that more traditional studies have had in differentiating specific drug-related risks. Further, the potential for disparaging a drug with irrelevant non-clinical safety concerns is real and may deny patients access to a truly life-saving medicine. Risk-monitoring strategies may be difficult to manage, increase costs, and possibly result in false information. Third-party payers may also be reluctant to support prospective monitoring of these risks.

Strategies that might improve patient care and increase the effectiveness of new therapies need to be explored. Workshops such as the Colloquium and those sponsored by the NCI and NHLBI have brought key stakeholders to the discussion, identified gaps in knowledge, and proposed actions to close these gaps. Furthering these discussions requires a close partnership between clinical and non-clinical oncology and cardiovascular experts and between regulators, academics, patients, research foundations, and drug developers. A venue and funding must also be identified. Nevertheless, the partnership between the HESI Cardiac Safety Committee, the cardio-oncology community, and other stakeholders can provide the foundation for substantially improving the safety and effectiveness of cancer treatment.

Conflict of interest

All authors declare there is no conflict of interest.

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