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Current Perspective

Cardiac safety evaluation in cancer clinical trials

Dorothy M. Gujral [a,b,*], Susan J. Cleator [a,b], Sanjeev Bhattacharyya [c,d]

[a] Department of Clinical Oncology, Imperial College Healthcare NHS Trust, London, UK
[b] Department of Surgery and Cancer, Imperial College, London, UK
[c] Echocardiography Laboratory, St Bartholomew's Hospital, London, UK
[d] Institute of Cardiovascular Sciences, UCL, London, UK

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Abstract Identification and quantification of the cardiac adverse effects of new cancer therapeutics is important when comparing treatment arms in clinical trials. Heart failure and left ventricular dysfunction are some of the most common adverse cardiac effects of a range of cancer treatments, including anthracyclines, trastuzumab and other targeted agents. Using the example of trastuzumab-induced cardiac dysfunction, we evaluated phase III clinical trials performed over the past decade to establish the methods used to identify heart failure and impairment of left ventricular function. Both these adverse events are difficult to accurately quantify. A clinical diagnosis of heart failure is subjective, and measurement of left ventricular ejection fraction has high interobserver variability depending on the method used to measure it. We found there was heterogeneity in methods used to diagnose both these adverse events. In addition, the use of quality assurance techniques to reduce measurement variability was low. We discuss and propose methods to standardise and reduce variability of cardiac event assessment in cancer clinical trials. This will allow true comparison of cardiac events between arms and trials with the aim of ensuring cardiac safety data are accurate.

There have been great advances in cancer treatment over the past decade. The survival of patients in both solid and haematological malignancies has increased and is likely due to a combination of better prevention, screening and treatment [1]. In human epidermal growth factor receptor 2–positive early breast cancer, the combination of surgery, radiotherapy and adjuvant chemotherapy leads to 10-year survival rates of up to

* *Corresponding author:* Department of Clinical Oncology, Imperial College Healthcare NHS Trust, Fulham Palace Road, London, UK.
E-mail address: d.gujral@nhs.net (D.M. Gujral).

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80% [2]. Heart failure and left ventricular dysfunction are the established risks of anthracycline and trastuzumab therapy. In the Herceptin adjuvant study, 1% of participants developed heart failure with a reduction in left ventricular ejection fraction (LVEF), and 4.4% developed an asymptomatic reduction in LVEF [2]. Current studies are evaluating whether reduced duration of therapy or biosimilars are non-inferior to the current standard of care [3,4]. When comparing the efficacy of new cancer therapeutics (with potential cardiotoxic effects), it is important to identify adverse cardiac events accurately. LVEF is the most common measure of cardiac function used in clinical trials [2]. However, there are multiple ways to measure LVEF using echocardiography (two-dimensional visual estimate, Simpson's biplane, three dimensional), each with different accuracies and variabilities [5,6]. A common threshold used for defining cardiac toxic events is a 10% reduction in LVEF [2]. Some techniques may not be adequate for clinical trials. For example, evaluation of LVEF by visual estimate can have a variability of up to 14% even in academic medical centres [7]. Therefore, it is important to make sure that assessment of LVEF during cancer clinical trials is performed with a technique with the lowest interobserver and intra-observer variability.

We examined the methods used to monitor LVEF as one important aspect of trastuzumab cardiac toxicity. We searched PubMed database for phase III, randomised clinical trials published in the last 10 years using the search terms 'early breast cancer' and 'trastuzumab'. The published manuscript and protocol was examined for cardiovascular assessment. This included the mode and method of monitoring, use of core laboratory and quality assurance standards. We identified eight phase III clinical trials incorporating 23,694 patients who fulfilled the selection criteria (Table 1) [2–4,8–12]. All studies included the measurement of LVEF as a marker of adverse cardiac events. All eight studies allowed multigated acquisition scan or echocardiography as the mode of measurement. However, no trial specified the method to measure LVEF or required the laboratory or personnel to have the relevant accreditation status. Two trials reviewed studies for LVEF using a core laboratory to measure reproducibility [2,4]. Three trials specified that serial studies were performed by the same laboratory/assessor [2,10,11]. The diagnosis of heart failure was made by the local study investigator in five trials and a cardiologist in three trials. Two trials included specific heart failure symptom questions during the trial follow-up visits.

Assessment of LVEF in clinical cancer trials is heterogenous with no standardised assessment of LVEF. Ideally, a technique that has low variability should be used. Cardiac magnetic resonance imaging has lower interobserver and intra-observer variability than echocardiography but is expensive and less widely available [13]. Echocardiography is the most widely available cardiac imaging modality. Trial protocols should specify the technique for measurement of LVEF; ideally, this should be two-dimensional Simpson's biplane or a three-dimensional volume method. Incorporation of techniques to reduce inherent measurement variability should be incorporated. These include appropriate credentialing of the laboratory and staff to ensure standardised images, protocols and measurement methods are followed [14]. Laboratory accreditation schemes mandate evaluation of readers against reference images and training programmes to reduce variability and therefore provide a mechanism to reduce variability [14,15]. Core laboratories can provide training and standard protocols to clinical sites, read studies at a central site, measure variability and provide feedback to improve imaging where needed [16,17]. Core laboratory–measured LVEF has reduced variance and improved reproducibility compared with clinical site–measured LVEF [18].

Evidence of congestive heart failure was evaluated during the study follow-up visits. However, there was a spectrum of methods used with some studies mandating specific questionnaires to actively identify heart failure symptoms, while others relied on patients to self-report symptoms. In addition, there was heterogeneity in whether a heart failure diagnosis was confirmed by the local site investigator or a cardiologist or cardiac safety committee. Congestive cardiac failure can be difficult to diagnose based solely on symptoms particularly in the early stages [19]. Symptoms such as dyspnoea or ankle swelling are non-specific. Usually a combination of symptoms together with biomarkers and evidence from cardiac imaging is required to make the diagnosis. Therefore, we propose a clinical event committee reviews and adjudicate the data [19].

At present, there are no universally accepted protocols for monitoring cardiac function during cancer therapy in clinical trials. The American Society of Clinical Oncology clinical practice guidelines suggest that routine surveillance in patients at risk of cardiac dysfunction is reasonable; however, they do not recommend a frequency [20]. The European Society of Cardiology (ESC) position article suggests that screening should occur according to local protocols but typically performed every 3 months [21]. In addition, there is no universal definition of cancer therapeutics–related cardiac dysfunction. The ESC defines this as a decrease in the LVEF of >10%, to a value below the lower limit of normal [21]. However, National Cancer Institute Common Terminology Criteria for Adverse Events does not specify an imaging-based value [22]. The lack of consensus may explain the variability between clinical trials.

In this article, we have focussed on trastuzumab-related cardiac dysfunction. More recently, development of myocarditis in patients treated with immune checkpoint inhibitors has been recognised [23]. The increasing