



## Commentary

## How can clinical research help our understanding of trastuzumab-related cardiotoxicity?

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It has been recognised that up to 25% of breast cancer overexpresses the transmembrane human epidermal growth factor receptor 2 (HER2), which, in the absence of treatment, is associated with an adverse prognosis for patients Hudis, 2007. The monoclonal antibody trastuzumab, which targets the HER2 receptor, has significantly improved both overall and disease-free survival for patients with advanced and early stage disease Slamon et al., 2001; Moja et al., 2012. However, an unexpected finding during the clinical trials of trastuzumab was the development of cardiotoxicity, mostly manifested as a decline in left ventricular ejection fraction (LVEF) and, more rarely, congestive heart failure. Despite extensive research, the mechanisms underlying trastuzumab-related cardiotoxicity remain poorly understood.

Against this background, the article in this issue of *EBioMedicine* by Reijers et al. Reijers and Burggraaf, 2015, investigated the effects of trastuzumab administration on a group of healthy male volunteers and its impact on cardiac function. This report focuses, in part, on a clinical trial, in which a developmental trastuzumab drug product was shown to have bio-equivalence to the currently approved formulation of trastuzumab (Herceptin®) Wisman et al., 2014. As part of this study, volunteers ( $n = 118$ ) underwent serial measurements of body weight and biomarkers, including haemoglobin, haematocrit, albumin, total protein, cardiac Troponin (cTn)-T and N-terminal pro-peptide of B-type natriuretic peptide (NT-proBNP), along with assessments of cardiac function by echocardiography. The current report focuses more narrowly on cardiac function in 54/118 men who received either trastuzumab ( $n = 46$ ) or placebo ( $n = 8$ ). Mean haemoglobin ( $-0.3$  mM), haematocrit ( $-0.013$  L/L), total protein ( $-2$  g/dL) and albumin ( $-2$  g/dL) all significantly decreased post exposure to trastuzumab compared with placebo. There was also a corresponding increase in body weight ( $+0.4$  kg), although this result was not statistically significant ( $p = 0.226$ ) and the time for change to return to baseline was not reported. There was no detectable increase in the cardiac specific blood parameters, NT-proBNP and cTn-T in either trastuzumab-treated volunteers ( $n = 46$ ) or those who received placebo ( $n = 6$ ). In a further subset analysis, there was no significant difference in LVEF in volunteers who received trastuzumab ( $n = 9$ ) compared to placebo ( $n = 8$ ) at either 4 or 63 days. No cardiac events were reported in the study, which is not unexpected, given the small number of subjects and exposure to trastuzumab was only a single dose.

The major strength of this report by Reijers et al. is the fact that the population were all healthy, with no comorbidities and had never been exposed to chemotherapy. In fact, many patients with HER2 positive breast cancer receive anthracyclines, which are also associated with a risk of cardiotoxicity. Hence the interpretation of the mechanisms underlying cardiotoxicity in this population is more challenging, and the current study represents a relatively homogeneous cohort, without the confounding effects of potentially cardiotoxic chemotherapy. The most interesting observation in this study was that trastuzumab was associated with an immediate, transient increase in body weight. The authors suggested that there was haemodilution caused by fluid retention post trastuzumab administration, and that this observation might provide some insight into the cardiovascular effect of trastuzumab. Furthermore, it was postulated that this might have been a direct consequence of cardiac myocyte stress induced by exposure to trastuzumab. However, the small placebo group (as comparator) limits this study and cautious interpretation of the findings is recommended. Although the authors concluded that monitoring of biomarkers and measuring body weight as used in the study might contribute to establishing a patient's risk of trastuzumab-induced haemodynamic alterations, the lack of a significant change in LVEF and the lack of correlation between haemodynamic alterations and cardiotoxicity, argues against the routine use of these measurements in clinical practice.

As noted, many patients with HER2 positive breast cancer receive anthracyclines, which can cause oxidative damage to cardiac myocytes. Those cells sustaining sufficient damage undergo apoptosis leading to cardiotoxicity, while other cells can repair the damage from these processes. If trastuzumab is then introduced, it binds to the damaged myocytes and inhibits cell repair thereby resulting in an even higher incidence of cardiac dysfunction Ewer and Ewer, 2010. Trastuzumab also can cause cardiotoxicity when administered as a single agent or with a non-anthracycline chemotherapeutic agent, albeit at a much lower incidence. The mechanism differs to that of anthracycline-related cardiotoxicity, evidenced by the evaluation of cardiac biopsy specimens after trastuzumab exposure, which do not show typical anthracycline ultrastructural changes Ewer et al., 2005. In addition, withdrawal of trastuzumab can reverse the cardiac effects, with LVEF improving in most patients and trastuzumab rechallenge often possible Guarneri et al., 2006. However, LVEF recovery is not universal and some patients will be left with significant cardiac dysfunction. Therefore, a major focus of ongoing research is the development of biomarkers to identify those patients at most risk.

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Research into potential biomarkers to predict risk of cardiotoxicity in patients treated with trastuzumab, including the study by Reijers et al., has focused on cTns, which are relatively specific for myocardial damage. However, results from clinical studies have been conflicting. Cardinale et al. identified a subgroup of patients treated with trastuzumab and elevated cTnI, who were more likely to develop trastuzumab-induced cardiotoxicity, less likely to recover fully and who had a 25-fold increase in risk for major adverse cardiac event [Cardinale et al., 2010](#). In contrast, in a prospective study investigating cTnI in patients treated with chemotherapy, trastuzumab and the oral anti-HER2 agent lapatinib, there was no association between elevations in cTnI and LVEF decline [Morris et al., 2011](#). Similarly, in the present study by Reijers et al., there was no increase in NT-proBNP and troponin-T post exposure to trastuzumab and no link to cardiotoxicity. In short, the clinical utility of these cardiac biomarkers in predicting trastuzumab-related toxicity is currently unclear.

Trastuzumab-induced cardiotoxicity remains an important clinical concern for all patients undergoing therapy for HER2 positive breast cancer. As evidence accumulates we are developing a clearer understanding of the pathophysiology of this important clinical problem. However, further research is needed to discover potential biomarkers, which will allow identification of those people at risk of developing cardiotoxicity and thereby, tailoring therapy (both anticancer and cardioprotective) to ensure that our patients achieve the optimal benefit of trastuzumab without the potential long term toxicity.

## Disclosure

The authors declare no conflicts of interest.

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