EDITORIAL

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Trastuzumab cardiotoxiciy: the age-old balance of risk and benefit

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The cardiac sequelae of trastuzumab administration has been the subject of considerable concern dating back to the original report noting a 27% incidence of ejection fraction declines and 19% of clinical heart failure (Slamon *et al*, 2001). Although this trial continues to be cited, these high incidences have never been subsequently encountered. As knowledge regarding how trastuzumab affects the heart expands, new questions arise. These questions run the gamut from whether trastuzumab truly exhibits primary cardiotoxicity to whether zealous monitoring of ejection fraction every 3 months offers any quantifiable benefit to patients in the form of furthering early intervention to delay overt cardiotoxicity (Davies *et al*, 2016; Ewer and Swain, 2016). Some findings regarding trastuzumab cardiotoxicity are sufficiently clear and have been observed over sufficiently long periods that they can, at least for the present, be taken as established facts. Trastuzumab is associated with cardiomyopathic events; these events are indisputably different from the primary toxicity seen with anthracyclines that destroy myocytes in a cumulative dose-related fashion. The mechanism or mechanisms of trastuzumab-associated cardiotoxicity are different; the structural changes seen with agents that show primary toxicity are absent, and there is increasing evidence that observed declines following administration of this agent are often, albeit not always, reversible (Ewer and Lippman, 2005). We now also have sufficient experience in treating patients with metastatic disease to understand that for many, albeit not all, the drug can be given for long periods of time without untoward cardiac events (Tripathy *et al*, 2004).

The mechanisms for what does occur in the heart are probably more complex than have been appreciated. Trastuzumab, as a monoclonal antibody that affects tyrosine kinase pathways, initially was not considered a likely agent for cardiotoxicity, and yet cardiac effects were clearly noted. One established mechanism involves interference with myocyte repair (de Korte *et al*, 2007). Damaged myocytes are less likely to recover in the presence of trastuzumab, offering a possible explanation of the reason higher levels of toxicity are noted when trastuzumab is given concurrently or immediately following an anthracycline (Ewer and Ewer, 2010). When the time interval between the two agents is sufficiently long so that cell damage from the anthracycline has resolved, trastuzumab-associated events are almost as low as is the case when an anthracycline has not been given (Suter *et al*, 2007).

We also recognise that some patients experience declines in their ejection fraction or experience overt heart failure after trastuzumab exposure. Are these events because of inherited predisposition, acquired sensitivity to the drug, some enhanced underlying myocyte injury for which cell repair is impaired, overzealous monitoring in the face of imperfect methods of determining ejection fraction, or some other as yet unexplored mechanism?

Trastuzumab has had a major impact on the treatment of HER-2-positive breast cancer. The agent is used in both the metastatic and adjuvant setting. Although patients with metastatic disease are often treated to progression or intolerance, the optimal duration of treatment in the adjuvant setting is not, or at least not yet, certain. The HERA trial looked at 1 *vs* 2 years of administration and found that the additional year offered no oncological advantage; however, more cardiac events were noted among the 2-year when compared with the 1-year cohort (20.4% *vs* 16.3%; Goldhirsch *et al*, 2013). Interference with cell repair could offer a plausible, albeit unproven, explanation.

It is in the context of these observations that we can explore the findings of Earl *et al* (2016) reported in this issue of *British Journal of Cancer*. In this highly important and timely initiative to determine if 6 months of trastuzumab is oncologically inferior to the usual 12 months of exposure, the Persephone trial was undertaken; cardiac function is a secondary end point of this trial, and is appropriately reported ahead of efficacy data that may take considerable time to be ripe for analysis.

The researchers took an approach to cardiac events that may have been overinclusive in that a new or altered cardiac medication prescribed during the 12 months after starting trastuzumab was considered sufficient for positive adjudication; overinclusion, if it

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occurred, would apply to both the 6- month and 12-month arms equally. Several of the reported findings reinforce our present understanding of trastuzumab-associated cardiotoxicity: first, more events were noted with longer exposure, a finding that was also seen in the HERA and PHARE population. This finding underscores that the mechanism, while not cumulative dose-related is, nevertheless, influenced by the duration of exposure. It is notable that doubling the time of exposure to trastuzumab did not double the risk of clinical cardiac dysfunction as defined by the authors. The 6-month arm found this end point achieved in 9% of patients compared with 12% in the 12-month arm. This finding suggests that cardiotoxicity is disproportionally attributable to earlier trastuzumab exposure. A shorter time interval after anthracycline exposure, equal in both arms, might in part explain these results, as injured cardiac myocytes could still be in a vulnerable state during the early period following anthracycline administration, and thus more sensitive to the effects of trastuzumab. This observation is consistent with HERA, where the 2-year incidence of cardiac events was 20% higher than in the 1-year population.

In addition, this study confirms several established risk factors for trastuzumab cardiotoxicity, including older age, prior cardiovascular disease, lower baseline ejection fraction, and higher cumulative anthracycline dose. Even mildly lower baseline ejection fractions may suggest previous cardiac insult with corresponding depletion in underlying reserves, making trastuzumab cardiotoxicity easier to unmask. By the same logic, older age, previous cardiovascular disease, and greater anthracycline exposure are likely to deplete cardiac reserves in a similar way.

A reduction in the ejection fraction may be the harbinger of serious or life-threatening heart failure, or it may be a temporary observation of little clinical consequence. Fortunately, notwithstanding the higher incidence of events reflected in the SEER data base regarding older women who are likely to have concomitant cardiac risk factors, we have little indication from the extensive measurements of this trial as well as others that large numbers of patients develop serious or life-threatening declines in cardiac function. Earl *et al* (2016) report here the incidence of symptomatic heart failure to be 4.4% in the 6-month arm and 6.4% in the 12-month arm. We are not given data on the severity of these clinical heart failure events. This modest incidence in symptomatic heart failure in the adjuvant trials and the reported late follow-up studies is a very comforting finding, underscoring the clinical observations that most patients treated with trastuzumab, when not given concomitantly with an anthracycline, tolerate the drug well. If they experience ejection fraction declines most recover, and those few who do develop devastating heart failure are both unusual and difficult to predict in advance. The fact that three cardiac deaths reported by Earl *et al* (2016) were all ischaemic likely reflects the background incidence of coronary artery disease in this population, independent of any trastuzumab effects.

So where does this report leave us? Can we answer some of the questions related to trastuzumab cardiac events? In taking in the calculus of risk and benefit, the benefit of trastuzumab is huge, the cardiac risks, although not trivial, are modest. The big question of the Persephone trial will then boil down to whether 6 months trastuzumab exposure, when compared with 12, is statistically inferior from an oncologic standpoint, and to what extent. As Earl *et al* (2016) point out, a highly important finding would be that 6 months of the monoclonal antibody demonstrated non-inferior oncologic efficacy to that of 12 months. This finding would help our patients in that they could end their treatment sooner, would probably need less cardiac monitoring, and would enjoy a less burdensome, less costly and equally effective therapy. If 12 months is superior from the oncologic perspective, Earl *et al* (2016) have reinforced our notion that fears of cardiotoxicity should not undermine optimal oncologic intervention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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