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Cardiotoxicity Monitoring Guidelines in Patients on Anti-HER2 Therapy

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Abstract

Introduction
Anti-HER2 therapies such as Trastuzumab carry warnings for cardiotoxicity, though cardiac assessment and monitoring remains an area of clinical debate. Utility of cardiotoxicity monitoring protocols in light of refined treatment regimens is unknown. The degree to which day-to-day clinical practice is informed by current guidelines is unclear.

Methods
A brief survey was designed to audit guideline awareness relating to cardiotoxicity prevalence and monitoring in breast cancer patients treated with HER2-targeted therapy amongst a representative cohort (n=10) of non-consultant hospital doctors (NCHDs) on the breast cancer surgical service in a large tertiary referral centre.

Results
Some lack of awareness of current guidelines across grades was evident, which likely reflects a disconnect between the theoretical guidelines and their clinical usefulness, as well as the relatively infrequent prevalence of cardiotoxicity. Although understanding of normal parameters was generally good (80% of NCHDs correctly recognising normal baseline LVEF as >55%), appropriate frequency of monitoring (12 weekly) was underestimated by 90% of this cohort (n=10). All respondents also underestimated the recommended frequency of monitoring in patients with cardiac impairment. Prevalence of cardiotoxicity was overestimated by all respondents. Although 90% of clinicians surveyed could suggest several assessment modalities, MUGA scans were not mentioned, despite being the method suggested in the Irish guidelines.

Conclusion
Cardiotoxicity is an infrequent but clinically important adverse event in the treatment of HER2-positive breast cancer patients. This small study suggests the timeliness of reviewing and potentially updating current guidelines to reflect imaging advances, as well as re-examining the criteria for scanning frequency in light of refined treatment protocols.

Introduction

Cardiotoxicity is an established clinical issue associated with the use of the HER2-targeted therapy Trastuzumab, though the mechanisms underlying this clinical problem remain unclear. Given the ever-growing prevalence of cardiac conditions in an aging population (the same population most at risk of developing breast cancer), healthcare providers continue to be wary of cardiac complications, which may range from asymptomatic decreases in left ventricular function to fulminant cardiac failure and arrest [1]. Moreover, as treatment efficacy improves and patients can expect to live longer, the long-term side effects of treatments such as Trastuzumab on cardiac health will become evident. A "risk- benefit" model may be employed, whereby the anticipated clinical benefit of therapies is weighed against risk factors for the development of cardiotoxicity (such as pre-existing cardiovascular disease, advanced age, concurrent cardiotoxic therapies etc.). In this framework, clinicians aim to maximise clinical benefit from anti-HER2 targeted therapies with due regard to potential risks.

Several mechanisms to explain drug-related cardiotoxicity have been proposed, most of which have been developed in the context of concurrent anthracycline and Trastuzumab treatment. Though anthracycline treatment exhibits a dose-dependent, irreversible cardiotoxicity and Trastuzumab-associated cardiotoxicity is broadly thought to be reversible, recent work has suggested that ultrastructural cardiac changes may persist after cessation of Trastuzumab therapy [2]. Thus, although a move away from concurrent anthracycline treatment is noted in our centre in line with Irish and international practice, Trastuzumab related cardiotoxicity remains a valid issue.

Trastuzumab (Herceptin) carries a boxed warning for cardiotoxicity advising the assessment of cardiac function before and during treatment; similarly, newer anti-HER2 targeted therapies such as Pertuzumab and lapatinib also carry warnings for potential cardiotoxicity. Although the development of milder forms of treatment-related cardiotoxicity do not represent an absolute contraindication to therapy, discontinuation of therapy in the short term is advised if a patient's LVEF falls below "institutional limits of normal", a $\geq$ 10% decrease in LVEF (compared to pre-treatment baseline), or an absolute decrease of $\geq$ 16% [3]. The metrics used to delineate clinically important outcomes are variable within the literature. Reported data on incidence and severity of Trastuzumab-associated cardiomyopathy varies somewhat across clinical trials. For example, when asymptomatic LVEF is considered, a decline of 10% is considered significant. 3% of participants in the HERA (Herceptin Adjuvant) study [4] were recorded to have significant LVEF drops (though only 2% had symptoms consistent with congestive cardiac failure); contrasting with 14% of patients in the NSABP-31 trial [5] and 18% of patients in the BCIRG 006 trial [6,7]. In terms of more serious events, one meta-analysis of five major Trastuzumab trials reported a rate of grade 3/4 cardiac toxicity events (inability to carry on any physical activity without discomfort) of 4.5% in Trastuzumab-treated patients [8]. Others have reported a seven-fold increase in relative risk of congestive heart failure in patients receiving Trastuzumab with chemotherapy [9]. An increase in absolute risk of grade 3 and 4 toxicity events varying between 0.4- 3.3%, with a relative risk of 5-10-fold has been described [7]. Adverse cardiac events are more frequently observed in the first three months of therapy in some studies, though there is not universal agreement on this [10].

Overall, the published rates of both asymptomatic LVEF decline and overt heart failure respectively in patients treated with anti-HER2 therapies remain low outside of the setting of anthracycline-based chemotherapy combinations or anti-HER2 therapy in combination with a taxane (3.2% and 0.5% respectively in one study) [11], 5.6% and 0.4% in another [12] (in combination with a taxane and cyclophosphamide).

One possible explanation for discrepancies in reported outcomes is the use of different imaging modalities. Multiple gated acquisition (MUGA) scans (using radionuclide ventriculography) were traditionally the monitoring modality of choice in cardiac monitoring during chemotherapy, due to their high levels of reproducibility [5]. This was the modality used in the NSABP B-31 trial, while the BCIRG-006 and HERA trials used both echocardiography and MUGA. Echocardiography, although safe and inexpensive, continues to show variability in both performance and interpretation [13].

Either MUGA or echocardiography is advised by the manufacturers of Trastuzumab, without any stipulation as to frequency; though more frequent monitoring is advised in the context of any abnormality [14]. In Ireland a baseline assessment of cardiac status is advised, with reassessments at successive 12-week intervals [15]. However, adherence to these recommendations worldwide is variable, with some large studies estimating that less than half of patients undergo guideline monitoring, particularly young patients at low risk of cardiac complications [16]. Other authors have reported similar findings even in an older cohort, with anthracycline therapy in addition to Trastuzumab being the main predictor of adherence to monitoring guidelines [17]. It is clear that there is a disconnect between theoretical guidelines informed by the early trials and everyday clinical practice. This disparity has implications for both exposure of patients with inadequate LVEF to excessive risk, but also for patients who may have treatment suspended inappropriately despite recovery of LVEF. Management decisions must also take into account the prognosis of individual patients, with younger patients often receiving more aggressive therapy. Conversely, patients with metastatic disease may undergo less frequent monitoring in the absence of any symptoms of cardiotoxicity, given the clear benefit of anti-HER2 therapy in this cohort [18]. This work therefore aimed to audit current clinician knowledge of cardiotoxicity monitoring in the context of anti-HER2 therapies

Methods

Clinician knowledge of cardiotoxicity guidelines (and associated parameters) in breast cancer patients treated with anti-HER2 therapy was assessed. Specifically, a brief six-question survey (**Figure 1**) was designed based on the parameters of the monitoring guidelines and reviewed by the senior author in order to conduct an audit on guideline awareness amongst a representative cohort (n=10) of non-consultant hospital doctors (NCHDs) regularly rostered to staff a breast cancer surgical service in a single large tertiary centre (Audit number CA643). Knowledge pertaining to cardiotoxicity prevalence, presentation and management in HER2-positive breast cancer patients treated with HER2-targeted therapy was assessed. NCHDs at all grades (house officer, registrar, specialist registrar) were recruited from an outpatient breast clinic over a period of two weeks. Staff at all NCHD levels were recruited as symptomatic patients may present to any grade. 100% of participants approached agreed to participate.

Knowledge of anti-HER2 therapy-associated cardiotoxicity in clinical staff

Question 1: Some anti-HER2 therapies are recognised as cardiotoxic, causing a decrease in left ventricular ejection fraction and a spectrum of clinical presentations, from asymptomatic to overt cardiac failure. What would you consider a normal LVEF? (Tick one)

- >40%
- >45%
- >50%
- >55%
- >60%
- >65%

Question 2: Echocardiography is a common imaging modality used to assess cardiac function. Are you aware of any other imaging modalities used to assess cardiac function?

……..

Question 3: How often should a patient **without** any cardiac impairment have an echocardiogram during their anti-HER2 therapy according to the Irish guidelines?

……..

Question 4: How often should a patient **with any cardiac impairment** have an echocardiogram during their anti-HER2 therapy according to the Irish guidelines?

……..

Question 5: At what LVEF % value do the Irish guidelines recommend withholding treatment?

……

Question 6: What percentage of patients treated with anti-HER2 therapies suffer any degree of associated cardiotoxicity?

…….%

Figure 1: Six-question survey

Results

Overall, the audit revealed a lack of awareness of the current cardiotoxicity monitoring guidelines across all grades of NCHD, which likely reflects a disconnect between the theoretical guidelines and their clinical utility in the current climate for breast cancer surgical care. Specifically, knowledge of normal baseline LVEF was generally good (**Figure 2**, with 8/10 NCHDs correctly recognising normal baseline LVEF as >55%). NCHD awareness of alternative imaging modalities to echocardiography was poorer; with no clinician mentioning the MUGA scan as an option despite the fact that it is the recommended option in Irish guidelines. However, 9/10 clinicians were able to suggest at least one alternative to echocardiography, with responses including MRI or CT angiography, ECG and cardiac MRI/CT.

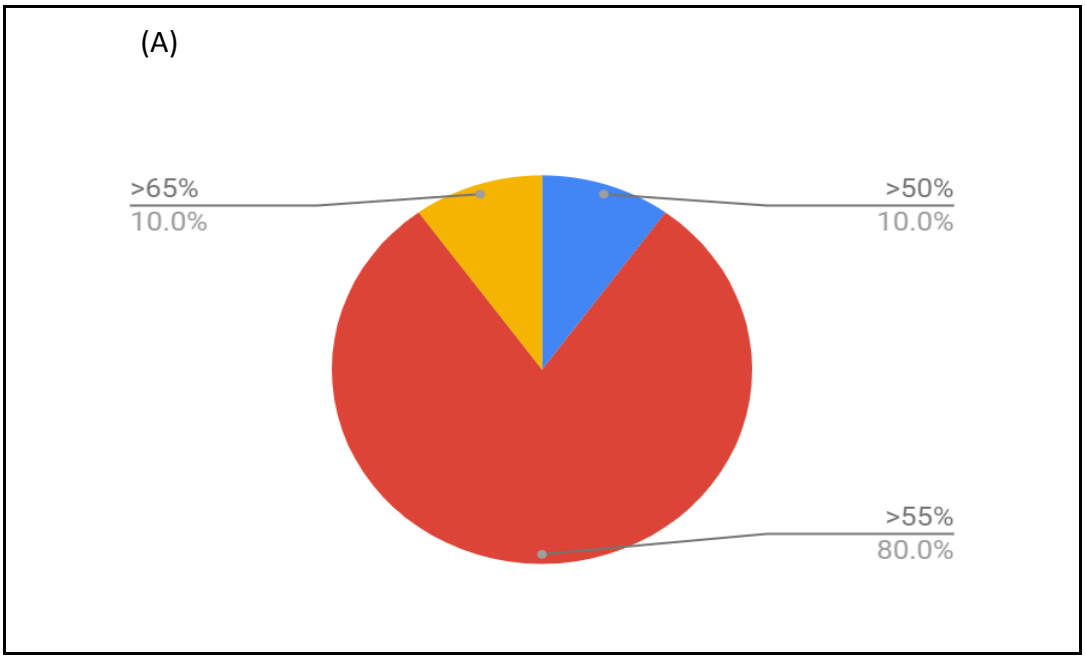

Figure 2: Estimation of normal LVEF (%) by NCHDs in Trastuzumab-related cardiotoxicity. Eight of ten (80%, red section) breast surgical NCHDs surveyed correctly estimated a normal LVEF to be >55%, with one minor over- and under-estimate of 65% and 50% respectively.

However, the recommended frequency of clinical monitoring was underestimated by this clinician cohort as compared to the Irish guidelines. In the context of Trastuzumab therapy for breast cancer patients, assessment every 12 weeks is advised [19]. However, NCHD estimates of cardiac function assessment frequency for patients without cardiac impairment ranged from 12 weeks to two years **(Figure 3)**. Similarly, monitoring of cardiac-impaired patients was underestimated at 2-12-monthly intervals as compared to the recommended 3-weekly interval. Half of respondents (n=5) estimated 6 monthly monitoring to be appropriate, with two respondents estimating annual monitoring to be appropriate in this context and one respondent for each of two- monthly and three- monthly; the final respondent was unsure.

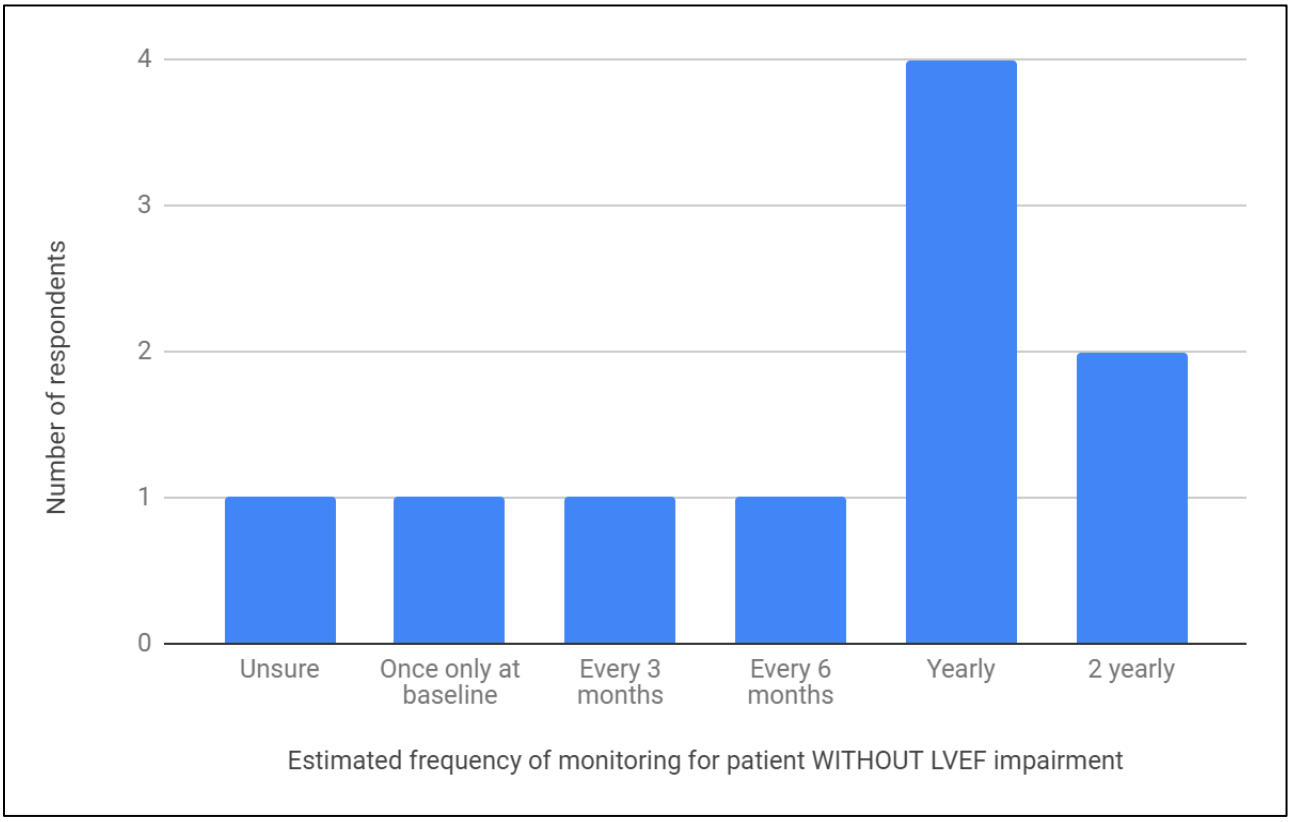

Figure 3: Frequency of appropriate LVEF monitoring in patients without left ventricular impairment was underestimated. NCHDs were asked to estimate the correct frequency of cardiac monitoring in patients with normal ventricular function and no impairment. Only one NCHD correctly estimated the frequency of LVEF monitoring in this patient cohort (every 3 months), with all other NCHDs underestimating the correct frequency.

When participants were questioned about threshold cardiac parameters mandating cessation of treatment, a wide range of absolute values was reported (**Figure 4**). Specifically, a range of values from LVEF of 15-45% was estimated, with only one NCHD correctly contextualising absolute LVEF value relative to baseline. Similarly, a wide range of estimates for the prevalence of any degree of cardiotoxicity in this patient population (including asymptomatic LVEF decreases) was noted. Interestingly, a range of values from 5-20% was returned, which represents an overestimation of risk. Three of ten NCHDs estimated a value of 5%, with a further three estimating a value of 20% and then remainder in between; the final respondent was unsure.

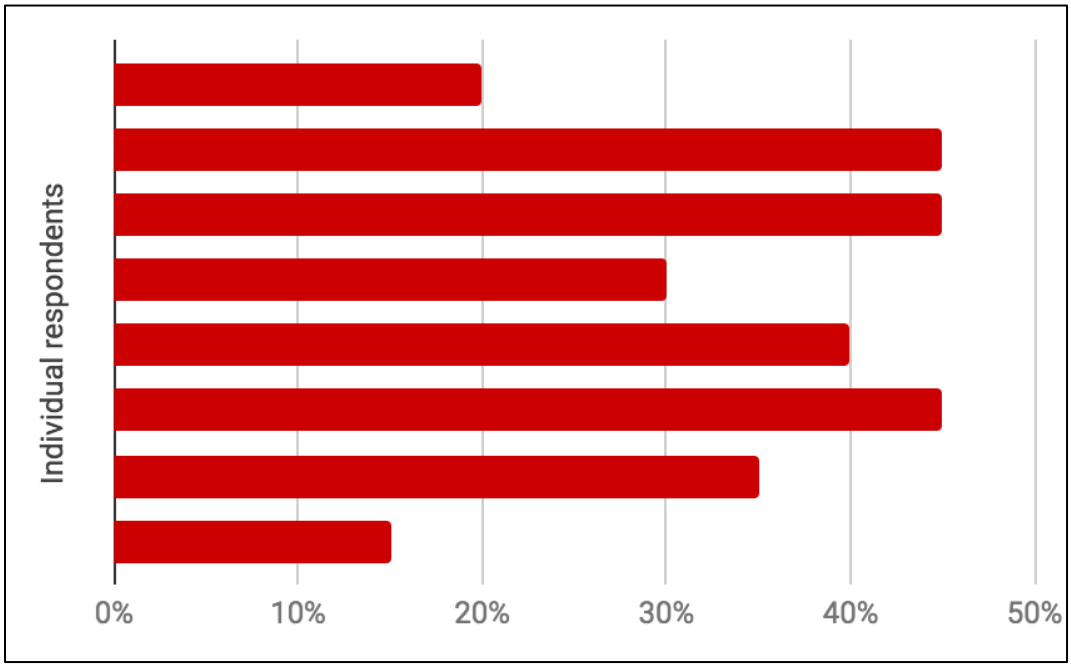

Figure 4: NCHDs reported a wide range of absolute LVEF % values at which treatment should be suspended. LVEFs between 15-45% were estimated by NCHDs (n=8; one further NCHD estimated a relative drop of 10% from baseline and one was unsure). Each individual bar represents a respondent.

Discussion

Cardiotoxicity remains a significant clinical issue in the use of Trastuzumab in HER2-positive breast cancer patients. Thus, this study sought to evaluate trainee clinician knowledge of the prevalence and also their broad knowledge of cardiotoxicity monitoring guidelines in practice.

One method of assessing the clinical significance of an LVEF decrease is to contextualise it within the trajectory of cardiac functioning and disease prognosis. Indeed, the Irish guidelines clarify that an "adverse event" (in an asymptomatic patient) mandating withholding of treatment involves a drop of 10 points from baseline to below 50%. The Irish guidelines also suggest that all such patients should be referred to a cardiology service [19]. UK guidelines advocate a similar approach, with an additional recommendation of formally assessing cardiac risk factors before commencing therapy, and modifying risk factors such as hypertension accordingly [20].

Knowledge of the clinical guidelines amongst NCHDs of all grades on the surgical service was variable, underlining the lack of routine day-to-day utility in the setting of cardiotoxicity as a rare side effect of therapy. In illustration of this point, no clinician mentioned the use of MUGA scan as an alternative to echocardiography, although the Irish guidelines specifically mention this. Indeed, MUGA scanning is decreasingly used in practice, given concerns regarding serial radiation exposure [21] and is not routinely available in this centre. Of note, almost all clinicians could suggest at least one alternative imaging modality, and newer technologies such as cardiac CT and MRI are a potential future avenue of treatment [22].

A wide variety of relative and absolute decreases in LVEF value were suggested by respondents, which may reflect the infrequency of clinically significant cardiotoxicity events in breast cancer patients receiving anti-HER2 therapies. It also reflects a criticism of the clinical utility of echocardiography itself and its potential for inter-observer variation (suggested to be as high as up to 14%) [23], as well as a broader debate regarding the degree to which asymptomatic LVEF decline predicts long-term cardiac safety outcomes [24].

This short study had several limitations, most notably a small sample size and a limited number of questions in the survey. Notwithstanding, as an exploratory study, it served to highlight potentially significant gaps in knowledge of cardiotoxicity monitoring among NCHDs on a busy surgical service; which merit further consideration. The extremely low frequency of presentations of symptomatic heart failure in breast cancer patients may explain the gaps in NCHD knowledge of the guidelines amongst surgical NCHDs. So too would the fact that cancer drug prescribing and monitoring mostly falls under the responsibility of the medical oncology service rather than the surgical service. Initial audit permissions were granted only for the surgical service; however, It would be of value to repeat this survey in a matched medical trainee population. Similarly, consultant awareness is likely much better than that of trainees, though formal assessment of this would be valuable, and the lack thereof is a shortcoming of this study. In conclusion, we suggest that it is timely to implement an educational intervention to increase adherence to the existing guidelines, perhaps in tandem with a review of their clinical relevance at a national level in the context of refined protocols and improved patient outcomes. An expanding portfolio of newer anti-HER2 therapies (such as Pertuzumab and kinase inhibitors) coming into common clinical use also carry the risk of cardiotoxicity. Of note, dual anti-HER2 therapy remains relatively well tolerated from a cardiotoxicity point of view, with significant data describing a minimally increased risk with the addition of further anti-HER2 drugs to existing therapeutic strategies, including in specific cardiac studies such as the TRYPHAENA safety study[25]. In this study, low rates of cardiotoxicity were seen in dual anti-HER2 therapy given with anthracycline or platinum-based chemotherapy, either sequentially or concomitantly, lending further weight to the practice of dual targeting. As expected, a slightly higher rate of ventricular dysfunction was seen in anthracycline containing regimens (5.3-5.6%) as compared to platinum containing regimens (3.9%). Thus, given the recognised side effect profile of anti-HER2 targeted agents, our study highlights that the issue of clinical monitoring, ongoing clinician education and implementation of clinical guidelines in an aging population remains of vital importance.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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