Real world impact of anti-HER2 therapy-related cardiotoxicity in patients with advanced HER2 positive breast cancer

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Introduction

Anti-HER2 therapies are the cornerstone of anti-cancer therapy for management of HER2 positive breast cancer. Their gradual introduction worldwide since the early 2000s has revolutionised the care of patients with HER2 positive advanced breast cancer (ABC), altering the natural history and improving survival (1). In early post-hoc analyses, patients receiving anti-HER2 therapies experienced higher rates of cardiotoxicity compared to historical controls and subsequent analyses have confirmed this association(1).

Anti-HER2 therapy-related cardiotoxicity most commonly manifests as an asymptomatic decrease in left ventricular ejection fraction (LVEF), usually defined as ≥10% reduction in LVEF from baseline (or ≥5% reduction from baseline if symptomatic) or LVEF below 50-55%(2). Anti-HER2 therapy-related cardiotoxicity can be of variable severity and is commonly reported to be reversible, unlike cardiotoxicity associated with anthracyclines (3). Emerging data suggests however, that improvement in LVEF does not necessarily equate with clinical resolution in this cohort of patients and this assertion needs ongoing investigation (4, 5). Cardiotoxicity is most commonly seen with trastuzumab, where it is reported to occur in up to 22% and 27% of patients when given concurrently with non-anthracycline-containing and anthracycline-containing chemotherapy regimens respectively (1, 2). A meta-analysis of subsequent adjuvant trastuzumab trials (including NSABP B-31, HERA, BCIRG-006, FinHer and NCCTG N9831), which adopted stricter enrolment criteria and studied almost 12,000 patients, reported an absolute risk of symptomatic cardiotoxicity of only 2.5% (6). Similarly, NSABP B-31 trial, cardiotoxicity of any severity occurred in only 4% of patients (7). Cardiotoxicity is also seen in association with other anti-HER2 therapies including pertuzumab, lapatinib and ado-trastuzumabemtansine (T-DM1), although less commonly than with trastuzumab based on current trial datasets (8-10).

Guidelines for cardiac risk assessment, drug prescribing and cardiac monitoring have been adopted in the adjuvant setting because of these observations. Patients treated with anti-HER2 therapy in the adjuvant setting, receive treatment for a discrete duration, typically 12 months, and the potential morbidity associated with permanent cardiac dysfunction is significant due to the curative-intent treatment and otherwise excellent long-term outcomes (11). Due to the unexpected detection of cardiotoxicity in the original ABC trials and the variable approach to cardiac monitoring in later trials, the optimal monitoring and management of cardiac toxicity in the ABC setting remains unclear. Arguably, patients in this group may receive greater clinical benefit from ongoing anti-HER2 therapies compared to patients receiving adjuvant treatment and therapy-related cardiotoxicity may be tolerated, particularly if asymptomatic (12).

Until October 2019, the Australian Pharmaceutical Benefits Scheme (PBS), which provides subsidised access to anti-HER2 therapy in the adjuvant and metastatic setting, mandated regular cardiac risk evaluation, with three-monthly multi-gated acquisition heart pool scans (MUGA) or transthoracic echocardiograms (TTE) to ensure all patients receiving anti-HER2 therapies, regardless of treatment intent, continued to have a baseline LVEF of >45% (13). Recently, the PBS relaxed their clinical criteria to require cardiac risk evaluation with MUGA or TTE at the commencement of therapy, with no mandated frequency of assessment thereafter for patients receiving treatment in both the adjuvant and metastatic setting. The Cancer Institute of New South Wales (NSW) and European Society of Cardiology (14) have recommended ongoing consideration of anti-HER2 therapy in patients at high risk of death from ABC, regardless of deterioration in LVEF or clinical symptoms. These recent changes in PBS prescribing criteria provide greater scope for treating physicians to recommend

ongoing therapy in patients that have an ongoing cancer response and may tolerate a degree of cardiotoxicity to yield ongoing clinical benefit from anti-HER2 therapy (15).

We here report a review of a prospective Australian registry, collecting comprehensive data on consecutive patients with HER2 positive ABC, the "Treatment of Advanced Breast Cancer in the HER2 positive Australian Patient" (TABITHA) registry. We examined the monitoring, incidence and management of anti-HER2 therapy-related cardiotoxicity prior to the recent prescribing changes with the aim of documenting real world outcomes for this patient group.

Material and methods

Using the TABITHA registry, patients with HER2 positive ABC diagnosed with metastatic disease and who commenced first-line therapy between 15th October 2006 and 29th October 2019 (at time of data cutoff) at nine Australian centres were retrospectively analysed. Each centre was individually recruited after the conception of the registry, thus the duration of enrolment varied between sites. Ethics approval for collection and utilisation of de-identified patient data was obtained from the participant sites, and from the ethics committee overseeing the TABITHA registry.

Patients were identified at their treating centre and data was extracted from medical records locally. Patients were not excluded on the basis of performance status, age or baseline cardiac function, however they must have been enrolled within three months of commencement of systemic therapy for ABC and eligible for PBS-subsidised therapy. Age and date at diagnosis of metastatic breast cancer, tumour details (histology include type and grade, hormone receptor status and HER2 status), metastatic sites, details of anti-HER2 and

other therapies in the metastatic setting, cardiotoxicity information (risk factors (14, 15), planned cardiotoxicity screening modality/frequency, incidence, severity and management), and date of death or last clinic follow-up were included.

Cardiotoxicity was defined as ≥10% reduction in LVEF from baseline or LVEF below 50-55% (or ≥5% reduction from baseline if symptomatic). There was no uniform definition applied for resolution of cardiotoxicity, although in general, this is expected to represent improvement in LVEF to >50% or to <10% decrease from baseline (7, 12).Risk factors for cardiotoxicity included age >70 years, previous chest wall irradiation, previous anthracycline exposure, previous anti-HER2 therapy-related cardiotoxicity (in the adjuvant setting), pre-existing cardiovascular disease and the presence of traditional cardiovascular risk factors such as hypercholesterolaemia, diabetes mellitus, cigarette smoking and obesity were documented for all patients (14, 15).

Simple statistical methods to determine medians and proportions were undertaken. Comparisons of patient characteristics were performed using the $\chi 2$ method. Statistical significance was defined as a two tailed p value ≤0.05. All statistical analyses were performed on SAS v6.1. Relationship between risk factors for cardiotoxicity and the incidence of cardiotoxicity were analysed post-hoc and were not pre-specified.

The TABITHA registry is sponsored by BioGrid Australia and has received financial support from Roche Products Pty Limited.

Results

Between 2006 and 2019, 312 patients treated at nine Australian centers, were included for analysis. Patient characteristics are summarised in Table 1. The median age was 57 years (range 28-96) and 311 were female (>99%). Most patients (59%) had hormone receptor positive disease and had originally received treatment for early breast cancer prior to developing ABC (n=173, 55%), which may have included chest wall radiation (n=34, 11%) and/or systemic therapies including anthracyclines (n=46, 15%) or anti-HER2 therapy (see table 1). The median follow-up period from diagnosis with ABC for the whole cohort was 28.3 months. [Table 1 near here]

The patients included in the TABITHA registry had a median of one risk factor for cardiotoxicity (range 0-5), with 22% aged >70 years, 15% with previous anthracycline exposure and 14% having pre-existing cardiovascular risk factors. The presence of risk factors did not appear to impact use of anti-HER2 therapy for those included in this registry. Most patients were monitored with MUGA or TTE (54% and 32%; remainder unknown) and a median baseline LVEF of 64% was recorded (range 49-79) (see table 1).

In total, 297 of 312 (95%) patients ultimately received systemic therapy for ABC. Of these, 287 (97%) received anti-HER2 therapy including dual HER2 blockade with trastuzumab*and*pertuzumab (77%), trastuzumab monotherapy (18%), T-DM1 (4%), pertuzumab monotherapy (<1%) or lapatinib (<1%) in the first-line metastatic setting. 260 patients (91%) received concurrent chemotherapy, most commonly with a taxane (90%) and only 12 (4%) received an anthracycline-containing regimen concurrently, although 46 (15%) had received prior anthracycline chemotherapy in the adjuvant setting. 112 (39%) patients

received concurrent hormonal manipulation with anti-HER2 therapy. Of the ten patients (3%) who did not receive anti-HER2 therapy, four received chemotherapy and six patients received only hormonal manipulation in the first-line setting, due to poor performance status and/or comorbidities.

Of the 287 patients treated with anti-HER2 therapy in the first-line setting, 17 experienced cardiotoxicity (6%). In 13 cases, this was asymptomatic dysfunction. Symptomatic dysfunction occurred in four patients (see figure 1). Cardiotoxicity was seen with both dual- (n=12, 71%) and single-agent HER2 (n=5, 29%) blockade. One patient who had documented cardiotoxicity (6%) was receiving an anthracycline concurrently, however five patients (30%) had previous anthracycline exposure in the adjuvant setting. Cardiotoxicity occurred after a median of 9.3 months (range 1.5-60; lower quartile 5.9 and upper quartile 15.8). There was compliance with PBS guidelines (current at the time of patient enrolment) in terms of planned monitoring frequency in 58% of patients in this group, compared to just 44% of the whole cohort. Baseline ejection fraction was 60%.

Detailed information regarding the specific management of cardiotoxicity in this group was not collected; however, of the 17 patients, 13 (76%) had anti-HER2 therapy withheld and 11 (65%) received cardiologist-directed management. Cardiotoxicity resolved on imaging in 11 patients (64%) after a median of 1.8 months (range 0.6-5.9). This included three patients in whom anti-HER2 therapy was continued and cardiotoxicity resolved (75%). Biomarkers, such as troponin, and additional echocardiographic metrics, such as global longitudinal strain were not consistently performed or collected.Of the 17 patients who experienced cardiotoxicity, nine (53%) continued on first-line anti-HER2 therapy, three (18%) went into second-line anti-HER2 therapy (all received T-DM1), one (6%) received second-line chemotherapy, three (18%) received hormonal manipulation alone after diagnosis with

cardiotoxicity and one patient (6%) received no further systemic therapy. There were no recurrent episodes of cardiotoxicity in these patients who received further anti-HER2 therapy in the first- or subsequent-line setting. Two patients (<1%) who did not experience cardiotoxicity upon exposure to anti-HER2 therapy in the first-line setting, experienced cardiotoxicity in the second-line when given further anti-HER2 therapy.

Patients developing cardiotoxicity did not differ in terms of age, Charlson comorbidity index or performance status when compared to patients not experiencing cardiotoxicity in a univariate analysis. However, patients who experienced cardiotoxicity were more likely to have ≥2 risk factors for cardiotoxicity (OR 3.9 95% CI 1.4-11.3 p= 0.01). The most common risk factor found in those developing cardiotoxicity was age >70 years (35%), although this risk factor alone was not associated with heightened cardiotoxicity risk (OR 1.7 95% CI 0.6-5.1) The only risk factor that was associated with risk of cardiotoxicity was a pre-existing diagnosis of cardiovascular disease (OR 7.1 95% CI 1.3-39.5 p= 0.03).

Discussion

Anti-HER2 therapy-related cardiotoxicity poses a significant challenge for medical oncologists and there is limited data available to guide the assessment and management of cardiotoxicity risk in ABC. The analysis of TABITHA registry data has demonstrated the nature of anti-HER2 therapy-related cardiotoxicity in an Australian “real life” population and provides reassurance for physicians that anti-HER2 therapy can be safely administered for most patients, even in patients with pre-existing risk factors for toxicity.

The addition of trastuzumab to standard chemotherapy revolutionised the care of patients with HER2 positive ABC following publication of the original trial in 2001 (1). Dual blockade

with trastuzumab*and*pertuzumab was shown to improve median overall survival further from 3.5 years to 4.7 years when compared to a trastuzumab and docetaxel combination (16). For patients with ABC, the risk of omitting life-prolonging anti-HER2 therapy therapies may therefore be greater than the morbidity associated with cardiotoxicity, unlike patients receiving anti-HER2 therapy in the adjuvant setting.

The patients analysed in TABITHA registry have similar demographic characteristics to the original trastuzumab and combined trastuzumab/pertuzumab ABC trials (1, 16), and other large retrospective reviews of patients receiving anti-HER2 therapy for ABC (17). Six percent of patients treated with first-line anti-HER2 therapy for ABC in the TABITHA registry developed cardiotoxicity. While under-reporting in our study remains a potential bias, and there were relatively low numbers of patients enrolled across a 13-year period, the data was collected prospectively using an agreed standard data set and data dictionary, and is further supported by other retrospective reviews (17, 18)and some clinical trial data (7).

Adherence to recommended screening guidelines, which existed at the time, was low, albeit in keeping with other retrospective reviews in which less than half of patients were screened accordingly (18). The reasons behind this are complex and beyond the scope of this study, however may have reflected the impact of Cancer Institute of NSW and to a lesser degree, the European Society of Cardiology on medical oncologists' practice in Australia and/or resource availability.

Cardiotoxicity was seen in patients with no risk factors for the condition, although was 3.9 times more likely in patients who had ≥2 risk factors. Reassuringly, despite the development of cardiotoxicity, 71% of patients were able to ultimately continue first- or second-line anti-

HER2 therapy and all received some form of ongoing systemic treatment. Conclusions with regards to impact on survival are unable to be drawn owing to small numbers and limited follow-up. Other reviews however have asserted that anti-HER2 therapy-related cardiotoxicity is not associated with inferior survival outcomes (17, 19) and it would be important to confirm this in our real world population going forward. .

The optimal cardiac monitoring strategy was not elucidated by our dataset, given the relatively low incidence of anti-HER2 therapy-related cardiotoxicity, low rates of guideline-adherent screening and ongoing LVEF reduction in 36% of the affected patients and may be best assessed in a clinical trial setting. It will be interesting to observe the approach that medical oncologists will take over the coming years to this complex problem in the environment of relaxed PBS prescribing rules and this data should be prospectively collected. Potential approaches may include regular monitoring for cardiotoxicity during the first 18 months of treatment,only in patients with ≥2 risk factors, or only when heart failure is detected.

Patients receiving anti-HER2 therapy for ABC are most likely to experience cardiotoxicity within the first 18 months of drug exposure (20). As found in this review, the median time was 9.7 months (and upper quartile 16.7 months). Therefore, closer monitoring with TTE for the toxicity during this high-risk period may be reasonable and would detect ~82% of patients. This could be further refined whereby only “high-risk” patients, ie. patients with ≥2 risk factors or a pre-existing diagnosis of cardiovascular disease are observed with cardiac imaging frequently during the initial stages of treatment. Given that most cases of cardiotoxicity were asymptomatic and the additional observation that there was no association between cardiotoxicity severity, resolution and access to subsequent treatment in our study however, a further argument could be made also to limit cardiac monitoring only

to patients who have (symptomatic) heart failure in patients with advanced breast cancer. Use of history and clinical examination, electrocardiograms and biomarker analysis with troponins may also be of benefit in stratifying at-risk patients at baseline (21).

A counterargument to the above would be to continue regular cardiac evaluation while receiving anti-HER2 therapy given the poor prognosis associated with heart failure. In fact, a diagnosis of cardiotoxicity *unrelated* to anti-HER2 therapy has been shown to have a median OS of just 2.1 years (22), compared to the median OS for HER2 positive ABC, which in clinical trial datasets is approaching five years. Aggressive treatment of asymptomatic changes to reduce the potential morbidity and/or mortality of a diagnosis of heart failure for a group with otherwise reasonable survival may therefore be recommended, and screening therefore required. With increasingly nuanced measures of cardiac surveillance, and comprehensive assessment including global longitudinal strain via TTE (and not MUGA), three-dimensional LVEF, cardiac magnetic resonance imaging and biomarkers such as troponins (14), the observed incidence of therapy-related cardiotoxicity may be greater in the future and as such, more of our patients may be impacted by the diagnosis.

Ultimately, the approach to anti-HER2 therapy-related cardiotoxicity should be a focus of ongoing clinical research and there will be ongoing debate with regards to the relevance of asymptomatic cardiotoxicity in the advanced breast cancer setting.

We would like to address several important limitations of our work. Firstly, this review was impacted by the lack of central review of the data, however all patients were assessed in accordance with standard guidelines. Furthermore, given the small numbers of patients developing by therapy-related cardiotoxicity, firm conclusions regarding the impact of

cardiotoxicity on survival are not possible. A larger review incorporating echocardiographic parameters (such as global longitudinal strain), actual (rather than intended) cardiac surveillance strategies, details of specific heart failure treatments and longer follow-up may help to answer this question.

Conclusion

The TABITHA registry provides a renewed understanding of the monitoring, incidence and management of patients experiencing anti-HER2 therapy-related cardiotoxicity during treatment for their HER2 positive ABC in Australia. Therapy-related cardiotoxicity was experienced by a small number of patients, however almost all were able to continue appropriate anti-HER2 therapy. The data raises important questions regarding the optimal cardiac monitoring strategy and deserves the attention of both medical oncologists and cardiologists, as patients continue to experience improved survival from ABC and the potential morbidity of heart failure could possibly have an increasing impact on their mortality.

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Table 1: Baseline characteristics

		Total (n=312)
Gender	Female	311 (>99%)
	Male	1 (<1%)
Age at diagnosis of metastatic disease (years)	Median (range)	57 (28-96)
Stage IV at initial diagnosis (%)	Yes	139 (45)
	No	173 (55)
ECOG performance status (%)	Median	0
	0-1	292 (94)
	2	14 (5)
	3-4	6 (2)
Charlson comorbidity index score	Median (range)	1 (0-10)
	0-1	168 (54)
	2-3	98 (31)
	>3	46 (15)
Hormone receptor	ER and/or PgR positive	184 (59)

status (based on most recent biopsy) (%)	ER/PgR negative		111 (36)
	Unknown		17 (5)
Planned cardiotoxicity monitoring modality and frequency of those receiving anti-HER2 therapy	Modality	MUGA	154 (54)
		TTE	92 (32)
		Unknown	41 (14)
	Frequency	3-monthly	133 (46)
		4-6 monthly	90 (31)
		Unknown/Other	64 (22)
		None	4 (2)
Baseline LVEF (by any modality) (%)	Median (range)		64 (49-79)
Risk factors for anti-HER2 therapy-related cardiotoxicity at baseline (%)	Number	Median	1
		0	155 (50)
		1	119 (38)
		2	31 (10)
		3-5	7 (2)
	Type	Age >70	71 (22)
		Previous exposure to anthracycline	46 (15)

		Previous chest wall radiation	34 (11)
		Pre-existing cardiac disease	7 (2)
		Other cardiovascular risk factors	44 (14)
		Previous anti-HER2-related cardiomyopathy	3 (1)

Table 2: Management of cardiotoxicity

			Total (n= 287)
Cardiotoxicity in first-line	Yes	All	17 (6)
		Asymptomatic	13 (5)
		Symptomatic	4 (1)
	No		270 (94)
			Total (n= 17)
Choice of systemic therapy in patients experiencing cardiotoxicity	Anti-HER2 therapy	Trastuzumab, plus pertuzumab	12 (71)
		Trastuzumab	5 (29)
	Concurrent chemotherapy	Anthracycline	1 (6)
		Other	15 (88)

Management of cardiotoxicity	Anti-HER2 therapy withheld		13 (76)
	Anti-HER2 therapy rechallenged		8 (62)*
	Cardiologist involved		11 (65)
Outcome of cardiotoxicity	Resolution	All	11 (65)
		Asymptomatic	9 (69)
		Symptomatic	2 (50)
	Ongoing	All	6 (36)
		Asymptomatic	4 (31)
		Symptomatic	2 (50)

*Plus an additional four patients (24%) where anti-HER2 therapy was not interrupted

Table 3: Univariate analysis for cardiotoxicity

Variable	Univariate	
	Odds ratio (95% CI)	P value
Cardiovascular risk factors: ≥2 vS 0-1	3.9 (1.4-11.3)	**0.01**
Charlson comorbidity index score: ≤3 vS >3	1.4 (0.4-5.1)	0.61
Age: <70 vS ≥70	1.7 (0.6-5.1)	0.33
Pre-existing cardiac disease	7.1 (1.3-39.5)	**0.03**
Prior anthracycline	2.4 (0.8-7.2)	0.12

Prior chest wall radiotherapy	1.8 (0.5-6.8)	0.35

Figure 1: Scheme for TABITHA patients