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Retrospective Cohort Study

Is there a window of opportunity to optimize trastuzumab cardiac monitoring?

Is there a window of opportunity to optimize trastuzumab cardiac monitoring?

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Abstract

BACKGROUND

It remains unclear whether the current arbitrary screening recommendations of trastuzumab-related cardiotoxicity provides an adequate balance between preventing heart damage and curtailing a curative treatment.

AIM

This study aimed to determine the incidence rate and consequences of trastuzumab-induced cardiotoxicity as adjuvant treatment in a real-world scenario.

METHODS

We present a retrospective analysis of cardiac function measured by echocardiogram at baseline and every 3 mo during trastuzumab treatment. Cardiotoxicity was defined as a drop on left ventricular ejection fraction (LVEF) ≥ 10% from baseline and/or any drop < 50%.

RESULTS

Between January/2011 and December/2014, 407 patients were selected, most (93.6%) were treated with an anthracycline followed by a taxane–based regimen and trastuzumab for 12 mo. Forty patients (9.8%) had cardiotoxicity, none of them symptomatic and 28 (72.5%) completely recovered LVEF. Cardiotoxicity happened early as shown by LVEF measured on echocardiogram 2 to 4 as compared to 5 to 7 (OR 2.47, 95%CI (1.09, 5.63), P = 0.024). There were 54 deaths (13.3%) during the 70-month follow-up period, 1 (0.2%) attributed to late cardiotoxicity (4 years after treatment). The absence of symptomatic cardiotoxicity during trastuzumab treatment and moreover, the early occurrence on the treatment period may translate into a strategy to evaluate less frequent

CONCLUSION

We observed a 9% rate of asymptomatic cardiotoxicity, which mirrors the results from the large adjuvant trials. Despite being transient, LVEF drop led to frequent treatment delays and interruptions. It remains unclear whether LVEF decline is predictive of late cardiotoxicity and treatment efficacy is compromised.

Key Words: Cardiac Toxicity; Ventricular Dysfunction; Heart Failure; Trastuzumab; Breast Cancer

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Core Tip: It remains unclear whether the current arbitrary screening recommendations for trastuzumab related cardiotoxicity in early-stage HER2-positive breast cancer provides an adequate balance between preventing heart damage and curtailing a curative treatment. Real world data showed that despite a low rate of mainly early, asymptomatic and transient cardiotoxicity, treatment delays and interruptions occur due to these findings. The study results suggest optimization of cardiac monitoring after an initial period without a decrease in cardiac function.

INTRODUCTION

Trastuzumab, a monoclonal antibody targeting HER2, represents a milestone in breast cancer treatment. The drug improves the progression-free and overall survival in metastatic and localized HER2-positive breast cancer.[1,2]

Cardiotoxicity remains the most compromising side effect.[3] Myocardial HER2 receptors are associated with cardiac function protection physiologically.[4] Therefore; the drug administration could lead to a decrease in left ventricular ejection fraction (LVEF),usually reversible, although a few patients need to delay or permanently stop their ongoing treatment.[4,5] The incidence of is around a quarter of patients receiving the drug, with a small percentage experiencing heart failure (1-4%).[6] Several factors can

contribute, such as the chemotherapy regimen, particularly anthracycline, patients' characteristics such as age, previous cardiovascular disease and low ejection fraction prior to treatment initiation.[7]

Cardiotoxicity of anti-cancer treatment includes any toxicity affecting the heart[8]and suggested by biomarkers, such as decrease on LVEF or signs of heart failure.[9]Guidelines suggest a baseline pre-treatment evaluation and risk stratification, during treatment monitoring and post-treatment surveillance.[2,10] Although these recommendations mimic the schedules used in the clinical trials, the cardiac assessment was not supported by prospective data.

Our study aimed to evaluate the cardiac function during trastuzumab treatment for early-stage breast cancer in a real-world scenario.

MATERIALS AND METHODS

Materials and methods:

A retrospective chart review was performed using patient`s medical files from January 2010 to December 2014, at the Instituto Nacional de Câncer, Brazil. Patients had tissue confirmation of HER2-positive breast cancer, stage I to III, treatment with chemotherapy combined with and followed by trastuzumab. Exclusion criteria included loss to follow-up in less than 3 mo after treatment initiation.

Echocardiogram was performed at baseline and every 3 mo during trastuzumab treatment. It was performed by the same examiner (METFC) and device - Siemens SONOLINE G 60, with P 4-2 cardiac probe (4,0 - 2,0 MHz). The analyses performed included the M-mode, 2D- mode, spectral doppler, colour Doppler and tissue doppler imaging. The cavities' dimensions were obtained according to the recommendation of the American Society of Echocardiography.[11] LVEF was calculated though the Teichholz Formulae.

Cardiotoxicity was defined as: 10% drop in LVEF from the baseline echo, a drop below 50% or symptoms according to the New York Heart Association (NYHA) class III or IV.[12,30]

The study was approved by the institutional review board and conducted in accordance to the Good Clinical Practice Guidelines and the Helsinki declaration.

Statistical analysis:

Numerical variables were reported by central tendency measures and categorical variables were represented by absolute frequency and percentages. A bar plot containing the percentage of cardiotoxicity detected by echocardiograms at each scheduled measurement was performed to describe differences between patients that developed cardiotoxicity.

A univariate analysis using the chi-square method for categorical variables and Two Sample T-test for continuous variables was initially performed to test the association between cardiotoxicity and potentially confounders' in clinical practice (age, comorbidities, body mass index (BMI)).

To verify statistical differences in cardiotoxicity during the follow-up time, Odds Ratio (OR) was performed to show differences in cardiac events odds in the beginning *vs* end of screening period. The prevalence's ratio was calculated using the Wald[13] and Score[14] methods. The R statistical software was used to calculate the odds ratio and prevalence measures using epiR package.[15]

RESULTS

From 423 eligible patients, sixteen were excluded (7 with metastatic disease and 9 Lost to follow-up), with 407 remaining for the final analysis.

The median age was 52 years and the body mass index (BMI) 27.54 kg/m^2. The stage at presentation was predominantly stage III: 59.47%. Most tumours were invasive ductal carcinoma (98,64%) and an anthracycline followed by taxane–based regimen was the most common treatment (93.6%). Almost all patients received trastuzumab for the whole one-year period (97%). (Table 1)

Table 1. Patients and treatment characteristics.

Forty patients (9.8%) had cardiotoxicity at a median time of 289 (114 - 680) days from treatment initiation and a wider variation of LVEF was seen on cardiotoxicity patients as shown by Figure 1 (b). Although none of these patients were symptomatic, all of them had their treatment delayed due to the echocardiogram findings. Twenty-nine patients (72.5%) recovered the LVEF, for which the drug was restarted, and 11 (27.5%) had trastuzumab suspended. The rates of cardiotoxicity did not vary according to age (P = 0.58), comorbidities (P = 0.81) or BMI (P = 0.64).

Figure 1 – Left Ventricular Ejection Fraction (LVEF) over trastuzumab cardiotoxicity monitoring in (A) total sample; (B) cardiotoxicity group.

Cardiotoxicity occurred early, as shown by Figure 2. The prevalence in echocardiograms 2 to 4 was 2.7% against 1.1% prevalence ratio in echocardiograms 5 to 7. The odds of cardiotoxicity were 2.5 higher when echocardiogram 2 to 4 were compared to echocardiogram 5 to 7 (OR 2.47, 95%CI (1.09, 5.63), P = 0.024).

Figure 2 – Percentage of cardiac event over time.

The median follow-up time was 70 mo and there were 54 deaths (13.3%). Overall, survival did not vary according to cardiotoxicity (P = 0.08). One death (0.2%) was

attributed to heart failure. However, it had occurred four years after the end of trastuzumab treatment, possibly related to late anthracycline cardiotoxicity.

DISCUSSION

We showed a 9.8% cardiotoxicity rate detected by routine echocardiogram, during trastuzumab-based treatment for early-stage breast cancer. To our knowledge, this is the largest real-world cohort reported in South America. Our results were similar to the ones presented by the large breast cancer adjuvant clinical trials 3 which varied from 6.0% to 35.4%.[16,17] This wide variation could be explained by the different chemotherapy regimens, but more likely attributed to patient selection and diverse definitions of cardiotoxicity.[18]

Whilst contemporary studies focus on predictive biomarkers (ie: plasma levels of troponin and/or brain natriuretic peptide) and more costly imaging studies (ie: cardiac magnetic resonance imaging), transthoracic echocardiogram is widely available with an affordable cost, which allows its widespread use.[19] Although the pathophysiology of cardiotoxicity is being elucidated and players such as neuregulin[20] have been suggested, reliable and validated biomarkers with a better cost-effectiveness than LVEF estimation are awaited.[21]

Recommendations to withhold Trastuzumab in Europe (absolute LVEF decrease > 20% or >10% to <50% or symptomatic heart failure)[22] and America (LVEF decrease ≥ 16% from baseline or LVEF below institutional limits of normality and ≥ 10% absolute LVEF decreased from baseline)[23] are roughly similar in not considering borderline asymptomatic decrease on LVEF. None of the patients on this cohort has had symptoms at the time of the abnormal echocardiographic findings. Notwithstanding, it led to treatment delays and interruptions based on the guidelines available. The consequences of asymptomatic LVEF drop are unknown as well as whether early trastuzumab treatment interruption may compromise its efficacy.[24,25] More recent trials showed less

clinical cardiac dysfunction in shorter as compared to longer trastuzumab treatment duration.[26]

There are known risk factors associated with trastuzumab-related cardiotoxicity such as age above 65, Ile655Val HER2 polymorphism, previous cardiovascular disease, radiation therapy and the use of anthracycline, especially high cumulative doses.[27,28] In our cohort, we were unable to show such a correlation. The studies on the other hand are conflicting about other factors such as other comorbidities (diabetes or kidney function impaired) or baseline LVEF (high or low).[3] We interpret these factors with caution once the standard of care population is significantly heterogeneous and frequently differs from the subjects included on clinical trials. Moreover, specific recommendation to adapt cardiac monitoring is lacking, unless the patient has a high cardiotoxicity risk.[29]

Of note, we showed an increased incidence of cardiotoxicity in the early monitoring as compared to the later cardiac function evaluation through echocardiogram. As there is a lack of prospective randomized clinical trials for optimal cardiac monitoring[309], our results provide an opportunity to such an endeavour.

Our study limitations included its retrospective nature, the limited number of patients and the lacks of standard reporting of comorbidities. On the other hand, similar studies suggest that a population to optimize monitoring might exist.[31]

CONCLUSION

The cardiotoxicity rates in a real-world population was similar to the ones reported by the large adjuvant trastuzumab trials. Most events occurred early during the initial monitoring examinations. As these findings led to treatment changes with unknown long-term consequences, these results deserve a prospective confirmation to assess the optimal way to monitor and manage trastuzumab-related cardiac events.

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