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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

IPOPORTO

Artigo de Investigação Médica

CARDIAC TOXICITY IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT TRASTUZUMAB

Lara Isabel Pires Luís

Orientador: Professor Rui Manuel Ferreira Henrique
Co-orientador: Professor António Miguel Henriques da Cunha Abreu

Porto, 2016

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Artigo de Investigação Médica

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Ano Letivo 2015/2016

Autora: Lara Isabel Pires Luís
Instituto de Ciência Biomédicas Abel Salazar
E-mail: lara_isabel_luis@hotmail.com

Orientador: Rui Manuel Ferreira Henrique
Professor Catedrático Convidado do Departamento de Patologia e Imunologia Molecular do Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto (ICBAS-UP)
Título profissional: Diretor do Serviço de Anatomia Patológica do Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. Porto; Diretor da Escola Portuguesa de Oncologia do Porto (EPOP); Investigador Sénior do Grupo de Epigenética e Biologia do Cancro, Centro de Investigação; Instituto Português de Oncologia do Porto (IPO-Porto) Francisco Gentil, E.P.E

Co-orientador: António Miguel Henriques da Cunha Abreu
Doutor em Ciências Médicas pelo ICBAS-UP
Título profissional: Assistente Hospitalar de Oncologia Médica do IPO-Porto

ACKOWLEGMENTS

I would like to express my heartfelt thanks to Professor Rui Henrique for giving me this opportunity and for all the support he provided.

I would like to thank Professor Miguel Abreu for helping me along these months, sharing the data of his patients and his knowledge on this theme.

To all who contributed for this investigation.

Finally, I would like to thank my family, specially my parents and sister, and my friends for the support through my life.

ACRONYMS

BMI-Body Mass Index

CD- Cardiac dysfunction

CHF - Congestive heart failure

EBC- Early breast cancer

ECHO- Echocardiography

FISH - Fluorescent in situ hybridisation

HERA trial - Herceptin Adjuvant (HERA) trial

HER2/ERB2 - Human epidermal growth factor receptor 2

IHC- Immunohistochemistry

LVEF- Left ventricular ejection fraction

MUGA- Multiple-gated scan

p value – Significance value

PHARE trial- Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial

HR- Hazard Ratio

SPSS - *Statistical Package for the Social Science*

SUMMARY

Background: Despite trastuzumab's efficacy against breast cancer with amplification of Her 2, it is also associated to risk of cardiac dysfunction namely when used with a chemotherapy regimen containing anthracyclines, whether at the same time or after.

Purpose: To evaluate acute cardiotoxicity of trastuzumab in breast cancer patients treated with adjuvant chemotherapy with anthracyclines, and to investigate possible predictors for this toxicity.

Patients and Methods: Retrospective review of clinical charts of 88 breast cancer patients treated with adjuvant chemotherapy regimen associated with trastuzumab. Data from patients and tumors characteristics, treatments performed and Left Ventricular Ejection Fraction (LVEF) measurements were analyzed, considering two patients groups defined according to the regimen of trastuzumab (concomitantly or sequential regimen, related to chemotherapy). Mann-Whitney test was used to compare continuous variables and Chi-square to compare categorical ones. The Cox regression model was used to evaluate association between variables (or factors) with cardiac events and to estimate HR with 95% Confidence Interval (CI). Significance was achieved when $p<0.05$.

Results: Fifty-eight patients (65.9%) received sequentially trastuzumab and 30 patients (34.1%) concomitantly with chemotherapy. The incidence of reduction of 10% LVEF occurred in 43.1% (25/58) in the sequential group and 50% (15/30) in the concomitant group (p=0.8). In the sequential group 13.8% (8/58) had left ventricular ejection fraction under <50% and in the concomitant group 10% (3/30)(p=0.6). Simultaneously reduction of 10% and < 50% LVEF occurred in 10.3% (6/58) of patients in sequential group and in 10% (3/30) of concomitant group (p=1). One patient (1.1%) had to discontinue treatment due to disease recurrence and 2 (2.3%) due to cardiac toxicity. Twelve patients (13.6%) held trastuzumab, 11 (12.5%) had asymptomatic decrease of LVEF and the other congestive heart failure (CHF), which reverted after holding trastuzumab. We did not find predictors for development of cardiac toxicity.

Conclusion: In our series cardiac events were rare. Most LVEF decreases were asymptomatic, with only one case of CHF.

Index Words: HER2 positive breast cancer, adjuvant trastuzumab, trastuzumab cardiotoxicity, Left ventricular ejection fraction, concomitant trastuzumab, sequential trastuzumab

RESUMO

Introdução: Apesar da eficácia estabelecida do trastuzumab no tratamento do cancro da mama com amplificação do oncogene HER2, está documentada uma frequência aumentada de disfunção cardíaca aquando do tratamento com antraciclinas, de forma sequencial ou concomitante.

Objetivos: Investigar toxicidade cardíaca aguda em doentes com cancro da mama tratadas com quimioterapia adjuvante com antraciclinas e quais os parâmetros preditores de toxicidade.

Metodologia: Estudo retrospetivo de 88 doentes do sexo feminino tratadas com quimioterapia adjuvante contendo antraciclinas, taxanos e trastuzumab. Foram recolhidas do processo clínico informações relativas a características demográficas, tumorais, de tratamento e medições da fração de ejeção do ventrículo esquerdo, definindo-se dois grupos de tratamento de acordo com o regime de trastuzumab (sequencial ou concomitante, em relação à quimioterapia). O teste de Mann-Whitney foi usado para comparar variáveis contínuas e o teste qui-quadrado para as variáveis categóricas. O modelo de Regressão de Cox foi usado para avaliar a associação entre variáveis (ou fatores) com eventos cardíacos e estimar o risco com Intervalo de Confiança a 95%. A significância era alcançada quando $p<0.05$.

Resultados: O regime sequencial foi usado em 58 doentes (65,9%) e o regime concomitante em 30 doentes (34,1%). Verificou-se redução de 10% na fração de ejeção do ventrículo esquerdo em 43,1% (25/58) das doentes do grupo sequencial e em 50% (15/30) das doentes do grupo concomitante (p=0.8). Reduções da fração de ejeção do ventrículo esquerdo para valores inferiores a 50% foram observadas em13,8% (8/58) das doentes do grupo sequencial e 10% das doentes do grupo concomitante (3/30) (p=0.6). A presença dos dois eventos anteriores de forma simultânea ocorreu em 10,3% (6/58) do grupo sequencial e em 10% (3/30) do grupo concomitante (p=1). Uma doente (1.1%) suspendeu tratamento com trastuzumab por recidiva da doença e 2 doentes (2.3%) por toxicidade cardíaca. Das 12 doentes (13,6%) que adiaram tratamento com trastuzumab, 11 (12,5%) fizeram-no por diminuição assintomática da fração de ejeção do ventrículo esquerdo e a outra por insuficiência cardíaca, que reverteu após adiamento do tratamento com trastuzumab. Não foi encontrada associação entre fatores descritos na literatura como preditores de toxicidade cardíaca e os eventos cardíacos registados nesta série.

Conclusão: Na nossa série, os eventos cardíacos foram pouco frequentes. A maioria das reduções na fração de ejeção do ventrículo esquerdo foi assintomática, registando-se um caso de insuficiência cardíaca.

CONTENTS

INTRODUCTION

Around the world, breast cancer is the most frequent cancer in women. In Portugal, in 2008, the estimated standardized incidence rate was 82.4 /100000.[1-4]

Amplification or overexpression of human epidermal growth factor receptor 2 (HER2), usually demonstrated by immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH), occurs in approximately 15-25% of invasive breast cancers and is associated with adverse disease prognosis and worse response to treatment[5].

Trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2 improves survival in patients with metastatic breast cancer and prolongs disease-free survival and overall survival in patients with early breast cancer (EBC).[5-8] The benefit of trastuzumab has been proven whether the antibody is given in an anthracycline-free regimen, concomitantly with taxanes or sequentially after chemotherapy[8].

The mechanism of action has not been completely understood but it is likely that increased levels of human epidermal growth factor receptor-2 expressed on the cell surface leads to increased intracellular tyrosine kinase activity and activation of signal transduction pathways, which inhibits apoptosis and promotion of cell growth, cell division, angiogenesis and metastasis.[5]

As a rule, trastuzumab is well tolerated but the predominant cardiovascular adverse effect is the induction of cardiac contractile dysfunction, a complication that has been previously associated mainly with anthracycline treatment. [6, 9] The HERA trial (adjuvant trial) reported a low incidence of cardiac events at 8 years of follow-up: 4.93% in the 1 year trastuzumab arm, as well as the reversibility of these events in most patients.[6]

Risk factors associated with trastuzumab cardiotoxicity include prior or concomitant anthracycline use, older patients, post menopausal status, hypertension/ use of anti-hypertensive medication, diabetes, pre-existing cardiac dysfunction and higher body index (>25 Kg/m^2)[10, 11]

Trastuzumab leads to cardiac dysfunction probably due to inhibition of ErbB2-ErbB4 signaling in the heart.[5] In this case and contrarily to antracyclines effect, there is no loss of myocardial cells, which are histologically normal, and the damage has high likelihood of reversion, resolving with discontinuation of the drug with or without cardiac medication [5, 10].

Patients treated with adjuvant trastuzumab should have periodic LVEF evaluation assessed by echocardiography or *multiple-gated scan* at baseline after completing anthracycline treatment, while on trastuzumab at 3-month intervals or sooner if CHF

symptoms develop, and after conclusion of trastuzumab at 6-month intervals until 24 months after the last dose of trastuzumab.[7, 10]

As detection and treatment of breast cancer is improving, survival is increasing and clinically relevant side effects, such cardiotoxicity, arise from adjuvant breast cancer therapy. Therefore, both short and long term follow-up of cardiac function is required for these patients.

The aim of this study was to retrospectively assess cardiac toxicity in female patients with breast cancer treated with chemotherapy based in anthracyclines and taxanes associated with adjuvant trastuzumab to define possible predictors for this toxicity.

METHODS

A retrospective study was designed to select female patients admitted to Instituto Português de Oncologia Porto (IPO Porto) between 2008 and 2010 for treatment of breast cancer with chemotherapy regimen containing anthracyclines and taxanes (FEC-D: 3 cycles of 5-fluouracil, epirubicin and ciclophosphamide followed by 3 cycles with docetaxel) and trastuzumab. Trastuzumab administration was considered in two regimens: after completion of chemotherapy (sequential scheme) or concomitantly (when was administered concomitantly with taxane).

Groups characteristics were not previously matched.

In all patients amplification of HER2 was demonstrated using Fluorescent in situ hybridization (FISH) or by Immunohistochemistry (IHC) technic as a surrogate of that.

Overall, 88 patients were included in this retrospective study and were grouped for analysis according to the therapeutic regimen: sequential (n=58) or concomitant (n=30).

Cardiac events assessed in this study were: congestive heart failure, decline of LVEF under 50%, 10% decline of LFEV from baseline, and cardiac-related death. Cardiac-related death was defined as death directly resulting from heart failure, myocardial infarction or documented arrhythmia within 24 hours after a cardiac event. Congestive heart failure was defined as symptomatic heart failure in the presence of a 10% decrease of LVEF or <50% from baseline.

The Mann-Whitney test was used to assess significant differences between groups (sequential vs concomitant) regarding age at diagnosis and median time until cardiac event, whereas Fisher Exact test was used for assessing differences in frequency of ECOG, estrogen and progesterone receptors, high blood pressure, type 2 diabetes, treatment with radiotherapy and previous cardiopathy among patients' subgroups.

The chi-square of Pearson test was used to assess differences in hormonal status of patients, comorbidity presence, body mass index (BMI), histologic type, grade, tumor and nodal status, type of surgery, axillary dissection, endocrine therapy and incidence of cardiac events.

The Cox regression model was used to evaluate association to cardiac events and to estimate HR with 95% Confidence Interval (CI). The level of significant was set at $p<0.05$.The data was analyzed using SPSS version 22.0.

This work was approved from the Ethics Committee of IPO Porto.

RESULTS

The demographic, clinicopathological and treatment characterization of each patients' groups is depicted in Table 1.

The median age of all patients was 53 years [range: 24-71 years] and are different between both groups, p=0.007, with older patients and more frequent in post menopausal state in sequential group (median 54 years [range: 24-70 years] and 70.7% (n=41) in menopausal state) compared to median of 47 years [range: 26-71 years, with 40% (n=12)] in concomitant group.

Most patients had good performance status compatible with ECOG: 0 in 94.5% (52/55) in sequential group and 96.7% (29/30) in concomitant group, p=0.5.

Most patients in both groups did not have past medical important issues - 75.9% (n= 44) of the sequential group and 80% (n=24) of the concomitant group, p=0.8. High blood pressure was present in 12% (n=7) in the sequential group and 10% (n=3) in the concomitant group, p=1. Type 2 diabetes was present in 5.2% (n=3) of patients in the sequential group and in 3% (n=1) of the concomitant group, p=1.

In the sequential group, 30.9% (n=17/55) of patient had normal BMI, 41.8% (n=23/55) were overweight and the remainder 27.3% were considered obese (n=15/55). In this last subgroup, 21.8% (n=12/55) were obese class I, 3.6% (n=2/55) obese class II and 1.8% obese class III (n=1/55). In the concomitant group, 38.5% (n=10/26) had normal BMI, 34.6% (n=9/26) were overweight and the remainder 26.9% were obese (n=7/26). In this last subgroup, 23.1% (n=6/26) were obese class I and 3.8% (n=1/26) obese class II. There are no differences in both groups regarding BMI, p=0.9.

Groups were balanced according to histologic type, grade, T (dimension) status, (p>0.05). Nodal status was different between the two groups, p=0.015, the concomitant group showed a tendency to N ≥ 2 tumours. Type of surgery, axillary dissection, radiation therapy and endocrine therapy were balanced between both groups, p>0.05.

CARDIAC TOXICITY ANALYSIS

Three of 58 patients (5.2%) in the sequential group received less than 18 cycles of trastuzumab. The reasons for this shorter treatment period included cardiac toxicity leading to early interruptions (n=2, 2.3%) and disease recurrence (n=1, 1.1%). All patients in the concomitant group completed 18 cycles of treatment.

Twelve of 88 patients held trastuzumab treatment (13.6%). The median time to holding trastuzumab was 22.5 weeks [range: 7 – 39 weeks] and the median time of holding was 19 days [range: 7 – 96 days]. In the sequential group 9 patients (15.6%) held the administration of trastuzumab and in the concomitant group 3 patients (10%) held treatment, p=0.5.

Table I Demographic, clinicopathological and treatment characteristics

		Sequential (n=58)	**Concomitant (n=30)**	**p value**
Age (years), n (%)	<40	4 (6.9%)	11 (36.7%)	0.002
	40-64	46 (79.3%)	17 (56.7%)	
	≥65	8 (13.8%)	2 (6.7%)	
Comorbidity, n (%)	No	44 (75.9%)	24 (80%)	0.8 [1]
	Previous cardiopathy	5 (8.6%)	3 (10%)	1.0
Histologic type, n (%)	Invasive carcinoma, NST	50 (86.2%)	27 (90%)	0.8
	Invasive lobular carcinoma	1 (1.7%)	0 (0%)	
	Mixed	6 (10.3%)	3 (10%)	
	Other	1 (1.7%)	0 (0%)	
Grade[2] , n (%)	1	1 (1.7%)	0 (0%)	0.1
	2	24 (41.4%)	6 (20%)	
	3	33 (56.9%)	24 (80%)	
Tumor size[3], n (%)	T1	29 (50%)	8 (26.7%)	0.1
	T2	26 (44.8%)	18 (60%)	
	T3	3 (5.2%)	4 (13.3%)	
Nodal status[3], n (%)	N0	14 (24.1%)	8 (26.7%)	0.015
	N1	32 (55.2%)	7 (23.3%)	
	≥N2	12 (20.6%)	14 (50%)	
Estrogen Receptors[4], n (%)	Negative	10 (17.2%)	6 (20%)	0.8
	Positive	48 (82.8%)	24 (80%)	
Progesterone Receptors[4], n (%)	Negative	19 (32.8%)	10 (33.3%)	0.8
	Postitive	39 (67.2%)	20 (66.7%)	
Surgery, n (%)	Mastectomy	17 (46.6%)	20 (66.7%)	0.1
	Lumpectomy	31 (53.4%)	10 (33.3%)	
Axillary Dissection, n (%)	No	13 (13.3%)	9 (30%)	0.4
	Yes	45 (77.6%)	21 (70%)	
Radiation Therapy, n (%)	No	5 (8.6%)	1 (3.3%)	0.7
	Yes	53 (91.4%)	29 (96.7%)	
Endocrine Therapy, n (%)	No	9 (15.5%)	6 (20%)	0.6
	Yes	49 (84.5%)	24 (80%)	

1-Absence of comorbidities *vs* presence of any comorbidity
2-Nottingham grading system
3-According to TNM staging system, AJCC 7th Edition
4-Cut-off used for positivity was ≥1% cells

In the sequential group, holding treatment occurred in 3 patients who had reduction of 10% and LVEF <50%, 1 patient that held treatment had LVEF <50% and 5 patients that held treatment had a 10% reduction. All patients were asymptomatic except for one that presented symptoms of CHF and recovered from this event after holding. The median time to holding was 21 weeks [range: 7- 30 weeks] and the median days of holding 28 days [range: 7 – 96 weeks].

In the concomitant group all patients had both reduction of 10% and LVEF <50% without symptoms of CHF. The median time until holding of trastuzumab was 26 weeks [range: 11 – 39 weeks] and the median time of hold was 14 days [range: 10 – 22 weeks]. There was no significant difference between both groups regarding time until trastuzumab hold (p=0.7) or duration of holding (p=0.3).

In the sequential group, suspension of treatment with trastuzumab occurred at 18 weeks and 45 weeks of treatment (median time: 31.5 weeks) due to sustained reduction of LVEF (reduction of 10% and LVEF <50%). Neither patients had symptoms of heart failure or had previous holding trastuzumab.

The incidence of cardiac end points is listed in Table II. Most events occurred during treatment, both in the sequential and concomitant groups.

There was no cardiac death reported and only one case of symptomatic CHF in the sequential group, that had a reduction of 10% and LVEF >50% recorded.

Reduction of 10% of LVEF occurred in 40 of 88 patients (45.5%), LVEF< 50% in 11 of 88 patients (12.5%) and reduction of 10% and LVEF<50% in 9 of 88 patients (10.2%). Reduction of 10% of LVEF was registered in 43.1% (n=25) of patients in the sequential group and in 50% (n=15) of the concomitant group, p=0.8.

The global median time until reduction of 10% in LVEF was 21.5 weeks [range: 3 – 55 weeks], whereas in the sequential group was 22 weeks [range: 8 – 55 weeks] and in the concomitant group 21 weeks [range: 3 – 53 weeks]. There was no significant difference in time until of 10% reduction in LVEF (p=0.6).

LVEF <50% was recorded in 13.8% (n=8) patients of the sequential group and 10% (n=3) patients of the concomitant group, p=0.6.

The global median time until LVEF <50% was 21 weeks [range: 7 - 55], corresponding to 24 weeks [range: 7 - 55] in the sequential group and 21 weeks [range: 10 - 26] in the concomitant group. There was no significant difference in time until LVEF <50% between both groups (p=0.6).

Simultaneous reduction of 10% of LVEF and LVEF <50% occurred in 10.3% (n=6) of patients in the sequential group and in 10% (n=3) of patients in the concomitant group, p=1.

The global median time until this event was 26 weeks [range: 10 – 55 weeks], corresponding to 28.5 weeks [range: 18 – 55 weeks] in the sequential group and 21

weeks [range: 10 – 26 weeks] in the concomitant group. There was no significant difference in time until this event (p=0.3).

Table II Summary of cardiac events.

	Sequential (n=58)	**Concomitant (n=30)**	**p value**
Cardiac death, n (%)	0 (0 %)	0 (0%)	-
CHF, n (%)	1 (1.7%)	0 (0 %)	-
Reduction of 10% LVEF baseline, n (%)	25 (43.1%)	15 (50%)	0.8
LVEF <50%, n (%)	8 (13.8%)	3 (10%)	0.6
Simultaneous reduction of 10% LVEF baseline and LVEF <50%, n (%)	6 (10.3%)	3 (10%)	1

Of note, in the sequential group, one patient had reduction of 10% and LVEF < 50% in the last cycle (at 55 weeks), without holding treatment. In the same group a patient who registered an LFEV <50% at 15 weeks of treatment was re-evaluated by a Cardiologist and maintained treatment.

PREDICTORS OF CARDIAC TOXICITY

There was no difference between trastuzumab regimen (concomitant), BMI >25 Kg/m^2, age >65 years, postmenopausal status, previous cardiopathy or presence of comorbidities and reduction of 10% of LVEF, reduction of LVEF <50%, reduction of 10% and LVEF <50%, as depicted in Table III.

Table III Univariate Cox Regression

	Reduction of 10%		**LVEF <50%**		**Reduction of 10% and LVEF <50%**	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Concomitant regimen	1.3 (0.7-2.5)	0.4	2.0 (0.5-9.1)	0.4	4.1 (0.7-24.9)	0.1
Age > 65 years	0.8 (0.4-1.8)	0.6	0.8 (0.1-7.0)	0.8	1.0 (0.1-9.0)	1
BMI >25 Kg/m^2	1.4 (0.7-2.8)	0.4	2.8 (0.3-23.1)	0.4	0.4 (0.1-3.7)	0.4
Previous cardiopathy	0.9 (0.3-2.7)	0.9	0.4 (0.0-3.5)	0.4	0.5 (0.1-4.0)	0.5
Post menopausal	0.6 (0.3-1.2)	0.2	0.3 (0.1-1.5)	0.2	0.2 (0.0-1.5)	0.1
Presence of comorbidities	1.2 (0.6-2.3)	0.7	1.2 (0.3-4.2)	0.8	1 (0.2-4.2)	1

DISCUSSION

The main goal of this study was to determine the profile of cardiac toxicity in breast cancer patients treated with adjuvant trastuzumab, using as cardiac events CHF, reduction of 10% of LVEF, LVEF <50%, concomitant reduction of 10% of LVEF and LVEF <50% as well as death events related to cardiac toxicity. Although no death due to cardiac toxicity was recorded, a case of CHF in the sequential group was identified**.**

In our study, reduction of 10% baseline occurred in 43.1% of the sequential group and in 50% of the concomitant group. These values are higher than the incidence in the 1 year arm of HERA trial (15.2%)[6]. It is noteworthy that although 10% reduction of LVEF baseline was frequent in both groups, only nearly 10% of both groups had concomitant LVEF <50% and only one patient suffered from CHF, which may indicate that not all early detections of 10% reductions are necessarily symptomatic and may not always lead to CHF.

The incidence of LVEF <50% was 13.8% in the sequential group and 10% in the concurrent group. These results are higher than the incidence registered on HERA trial (3.9%)[6] and the incidence of 12-month arm of the PHARE trial (6.3%)[12].

In our study, the incidence of reduction of 10% and LVEF <50% is similar in both groups, nearly 10%, and is higher than the incidence of the same event in the PHARE trial (4.8%) and HERA trial (3.2%)[12].

We must be cautious when comparing these results with published data. In the HERA trial, patients of the 1 year trastuzumab were younger (median age 49 years) and only 26% of patients had previous chemotherapy with anthracyclines and taxanes (6.1% concomitant and 19.9% sequential)[7]. In the PHARE trial, 73.9% of patients of the 1-year arm received a regimen with anthracycline and a taxane and the most used type of administration of trastuzumab was concomitantly (56.9%)[12].

This difference might be due to some of the limitations of our study, namely the small sample size and its retrospective nature.

In this study, the majority of events occurred during the period of treatment with trastuzumab, which is consistent with the results of the main clinical trials that tested adjuvant trastuzumab[6, 13].

Regarding the 3 patients (3.4%) who discontinued trastuzumab, 1 patient (1.1%) had to discontinue treatment due to disease recurrence and 2 (2.3%) due to cardiac toxicity. This fact is consistent with HERA trial results, in which discontinuation of trastuzumab due to recurrence of disease occurred in 4.1% of patients and due to cardiac toxicity in 4.3% of the trastuzumab arm[14].

From the 12 of 88 patients who held treatment, 1 (1.1%) presented cardiac symptoms (CHF) and 11 were asymptomatic (8 in the sequential and 3 in the concomitant group). Together with the 2 asymptomatic patients who suspended trastuzumab due to cardiac toxicity, treatment was held or suspended in 13 (14.8%) asymptomatic patients. These are lower rates compared to NSABP B-31 trial's, in which 8% of patients who temporarily held or permanently discontinued trastuzumab had symptomatic cardiotoxicity and 24% asymptomatic declines in LVEF[13], which might be due to the smaller sample

size of our series. As expected, the only case of CHF was reverted after holding trastuzumab[13].

Unlike previous studies, we found no evidence that older patients (age>65 years), previous cardiopathy, BMI >25 Kg/m^2 and comorbidity presence were risk factors for a cardiac event[10]. This might reflect the smaller sample size, not enabling statistical power to pinpoint differences, but it should also be emphasized that most patients treated with these regimens were selected based on their fitness to endure chemotherapy. Thus, it should not be surprising that most patients were relatively young (most of them aged between 40-65 years) and without significant comorbidities, as well as with a good performance status (ECOG 0 and 1).

Long-term data from HERA and N9831 B-31 trials suggest that cardiotoxicity is uncommon and generally reversible [6, 15]. Research in this field is warranted because women treated with adjuvant trastuzumab and that develop cardiotoxicity might live longer and with lower functional capacity. Moreover, toxicity itself may reduce future therapeutic options in patients that might present disease recurrence.

In summary, in our series cardiac events were rare and most LVEF decreases were asymptomatic and did not translate in CHF. There was only one case of CHF, reverted after holding treatment. In the future it would be interesting to expand the series and assess the long-term cardiotoxicity of these patients.

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RESUMO DO TRABALHO

INTRODUÇÃO

A amplificação ou sobreexpressão do *human epidermal growth factor receptor 2* (HER2), habitualmente demonstrado por imunohistoquímica (IHC) e/ou hibridação in situ fluorescente (FISH), ocorre em aproximadamente 15-25% dos carcinomas invasores da mama e está associado a prognóstico e resposta ao tratamento desfavoráveis.[5]

O trastuzumab, um anticorpo monoclonal dirigido contra o domínio extracelular do HER2, incrementa a sobrevivência das doentes com cancro da mama metastizado e prolonga o tempo livre de doença e sobrevivência global em doentes com cancro da mama precoce.[5-8] Este benefício está demonstrado na sua administração num regime de quimioterapia sem antraciclinas, concomitantemente com taxanos ou sequencialmente após quimioterapia.[8]

Geralmente o trastuzumab é bem tolerado, mas o principal efeito cardiovascular adverso é a indução de disfunção da contractilidade cardíaca, uma complicação também já conhecida do uso das antraciclinas.[6, 9] O estudo HERA (ensaio adjuvante) reportou uma taxa baixa de eventos cardíacos aos 8 anos de seguimento de 4,93% no grupo de tratamento a 1 ano e reversibilidade dos eventos na maioria dos doentes.[6]

Os fatores de risco associados à toxicidade cardíaca do trastuzumab incluem uso prévio ou concomitante de antraciclinas, idade avançada, estado pós-menopausa, hipertensão/uso de antihipertensores, Diabetes *Mellitus*, disfunção cardíaca prévia e índice de massa corporal aumentado (IMC>25 Kg/m2)[10, 11]. O mecanismo de disfunção cardíaca do trastuzumab provavelmente relaciona-se com a inibição da via de sinalização ErbB2-ErbB4 no miocárdio.[5] Neste caso, e contrariamente ao efeito das antraciclinas, não existe necrose miocárdica e o dano tem elevada probabilidade de reversão, resolvendo com a suspensão do agente com ou sem medicação.[5, 10]

O objetivo deste estudo foi avaliar retrospetivamente o perfil de toxicidade cardíaca em doentes do sexo feminino com cancro da mama tratadas com quimioterapia contendo antraciclinas, taxanos e trastuzumab adjuvante, bem como definir possíveis factores preditores desta toxicidade.

MÉTODOS

Foram selecionadas doentes do sexo feminino com cancro da mama tratadas no Instituto Português de Oncologia Porto (IPO Porto) entre 2008 e 2010 com quimioterapia contendo antraciclinas e taxanos (FEC-D: 3 ciclos de 5-fluouracilo, epirrubicina e ciclofosfamida seguida de 3 ciclos com docetaxel) e trastuzumab. A administração de trastuzumab foi considerada em dois regimes: sequencial (após completar quimioterapia) ou concomitante (quando administrado simultaneamente com taxano).

As características dos dois grupos não foram previamente emparelhadas. Todas as doentes tinham amplificação de HER2 demonstrado por FISH ou por IHC. No total, 88 doentes foram incluídas neste estudo retrospetivo e foram agrupadas de acordo com o regime terapêutico: sequencial (n=58) ou concomitante (n=30).

Os eventos cardíacos avaliados neste estudo foram: insuficiência cardíaca, diminuição da fração de ejeção do ventrículo esquerdo (FeVE) abaixo de 50%, diminuição de 10% do FeVE basal, e morte de causa cardiogénica. Esta foi definida como morte resultante diretamente de insuficiência cardíaca, enfarte do miocárdio ou arritmia documentada em 24 horas após um evento. Insuficiência cardíaca congestiva foi definida como insuficiência cardíaca sintomática na presença de diminuição de 10% da FeVE ou abaixo de 50% do basal.

O teste de Mann-Whitney foi usado para avaliar diferenças significativas entre os grupos em relação à idade ao diagnóstico e mediana de tempo até evento cardíaco, teste de Fisher na avaliação de diferença no ECOG, recetores de estrogénio e progesterona, hipertensão arterial, Diabetes *Mellitus* tipo 2, tratamento com radioterapia e cardiopatia prévia. O teste Q-quadrado foi usado para avaliar diferença no estado hormonal dos doentes, presença de comorbilidades, índice de massa corporal, tipo histológico, grau, T e N, tipo de cirurgia, esvaziamento ganglionar, terapêutica endócrina e incidência de eventos cardíacos. O modelo de Regressão de Cox foi usado pra avaliar a associação de eventos cardíacos e estimar o risco com intervalo de confiança de 95%. O nível de significância foi estabelecido para $p<0.05$. Os dados foram analisados através do programa SPSS versão 22.0.

Este trabalho teve aprovação do Comité de Ética para a Saúde do IPO Porto.

RESULTADOS

A caracterização demográfica, patológica, bem como os tratamentos efetuados pelos pacientes incluídos neste estudo estão descritos na Tabela 1.

A mediana de idade de todas as doentes foi 53 anos (intervalo: 24-71 anos), sendo uma diferença significativa, p=0,007, sendo que no grupo sequencial as doentes eram mais velhas e encontravam-se na menopausa (mediana de idade 54 anos

(intervalo: 24-70 anos) e 70,7% (n=41) em menopausa quando comparadas com as doentes do grupo concomitante [mediana de 47 anos (intervalo: 26-71 anos, 40% em menopausa)].

A maioria das doentes tinha um bom estado geral, compatível com ECOG: 0 em 94,5% (52/55) das doentes do grupo sequencial e em 96,7% (29/30) do grupo concomitante. A maioria das doentes nos dois grupos não tinha antecedentes pessoais de relevo – 75,9% (n= 44) no grupo sequencial e 80% (n=24) do grupo concomitante. Doze porcento (n=7) das doentes do grupo sequencial tinham hipertensão arterial e no grupo concomitante 10% (n=3). No grupo sequencial 5,2% das doentes (n=3) tinham Diabetes Mellitus e no grupo concomitante 3% (n=1).

Os dois grupos eram semelhantes na distribuição de hipertensão arterial, Diabetes Mellitus, tipo e grau histológico, estadio T (tamanho), tipo de cirurgia, realização de esvaziamento axilar, radioterapia ou hormonoterapia ($p>0,05$). A avaliação do estadio N (ganglionar) foi estatisticamente diferente, $p=0,015$, com tendência no grupo concomitante para $N\geq 2$.

No grupo sequencial 3 doentes (5,2%) realizaram um número inferior a 18 ciclos de tratamento com trastuzumab por recidiva da doença (n=1; 1,1%) e toxicidade cardíaca (n=2; 2,3%). Todas as doentes do grupo concomitante completaram os 18 ciclos de tratamento. Doze doentes adiaram tratamento (13,6%), numa mediana de 22,5 semanas (intervalo: 7-30 semanas) e duração média de adiamento 19 dias (intervalo: 7-96 dias). No grupo sequencial 9 doentes adiaram tratamento (15,6%) e no grupo concomitante 3 doentes (10%), $p=0.5$.

No grupo sequencial, o adiamento ocorreu em 3 doentes que apresentaram redução de 10% da FeVE basal e FeVE< 50%, 1 doente apresentou FeVE< 50% e 5 doentes apresentaram redução de 10% da FeVE basal. Todas as doentes estavam assintomáticas excepto uma que apresentou sintomas de insuficiência cardíaca congestiva (que reverteu posteriormente, após o adiamento). Todas as doentes do grupo concomitante que apresentaram redução de 10% da FeVE basal estavam assintomáticas. No grupo sequencial, a suspensão do tratamento com trastuzumab ocorreu devido a redução sustentada da FeVE (redução de 10% da FeVE basal e FeVE <50%) assintomática às 18 semanas e às 45 semanas de tratamento (mediana 31,5 semanas).

A incidência dos eventos cardíacos encontra-se na Tabela 2. Uma redução de 10% da FeVE basal ocorreu em 40 de 88 doentes (45,5%), FeVE < 50% em 11 de 88 doentes (12.5%), e simultaneamente redução de 10% da FeVE basal e FeVE < 50% em 9 de 88 doentes (10,2%). No grupo sequencial 43,1% (n=25) das doentes registaram redução de 10% da FeVE basal e no grupo concomitante 50% (n=15), $p=0.8$. FeVE < 50% ocorreu em 13.8% do grupo sequencial (n=8) e em 10% do grupo concomitante (n=3), $p=0.5$. Redução simultânea de 10% da FeVE basal e FeVE <50% ocorreu em 10,3% (n=6) das doentes no grupo sequencial e em 10% (n=3) das doentes no grupo concomitante, $p=1$.

PREDITORES DE TOXICIDADE CARDÍACA

Não foi encontrada nenhuma associação entre esquema concomitante de trastuzumab, índice de massa corporal >25 Kg/m^2, idade >65 anos, menopausa, cardiopatia prévia ou presença de comorbilidades e redução de 10% da FeVE basal, FeVE <50% ou, em simultâneo, redução de 10% da FeVE basal e FeVE <50%. As associações entre as variáveis e eventos cardíacos estão registados na Tabela III.

DISCUSSÃO

No presente estudo, redução de 10% da FeVE ocorreu em 43,1% do grupo sequencial e em 50% do grupo concomitante, sendo a incidência do grupo sequencial menor do que as encontradas no grupo de tratamento com trastuzumab (1 ano) do estudo HERA (48,9%) enquanto que a incidência do grupo concomitante foi semelhante.[6] Apesar da redução de 10% ser frequente nos dois grupos, aproximadamente 10% em ambos os grupos apresentavam simultaneamente FeVE <50% e apenas 1 doente manifestou insuficiência cardíaca congestiva, o que pode indicar que nem todas as deteções precoces de redução de 10% são necessariamente sintomáticas e que vão evoluir para insuficiência cardíaca.

A redução de FeVE <50% teve uma incidência de 13,8% no grupo sequencial e 10% no grupo concomitante, valores superiores ao do estudo HERA (3,9%)[6] e do que no grupo de tratamento de 12 meses do estudo PHARE trial (6,3%).[12]

Neste estudo, a incidência da redução de 10% e FeVE <50% é semelhante nos dois grupos, aproximadamente 10% e mais elevada do que a incidência descrita para o mesmo evento no estudo PHARE (4,8%) e no estudo HERA (3,2%). [12].

Ao compararmos estes resultados devemos ter em atenção alguns aspetos. No estudo HERA, as doentes do grupo de 1 ano de trastuzumab eram mais jovens (mediana de 49 anos), só 26% das doentes tinham realizado previamente quimioterapia com antraciclinas e taxanos (6,1% em esquema concomitante e 19,9% em esquema sequencial).[7]

No estudo PHARE, 73,9% das doentes do grupo de 12 meses de trastuzumab tinham realizado quimioterapia com antraciclinas e taxanos e a maioria havia sido administrada em esquema concomitante (56,9%).[12] Estas diferenças podem dever-se a algumas limitações no nosso estudo, nomeadamente o menor tamanho da amostra e a sua natureza retrospetiva.

Relativamente às 3 doentes (3,4%) que não concluíram o tratamento com trastuzumab, 1 doente apresentou recidiva da doença (1,1%) e 2 suspenderam por toxicidade cardíaca (2,3%). No estudo HERA, o trastuzumab foi suspenso por recidiva da doença em 4,1% das doentes e devido a toxicidade cardíaca em 4,3% das doentes[14].

Das 12 doentes que adiaram tratamento, 9 pertenciam ao grupo sequencial. Neste grupo, 1 doente apresentou insuficiência cardíaca congestiva enquanto todas as outras permaneceram assintomáticas. No grupo concomitante, todos os adiamentos foram devidos a reduções da FeVE assintomáticas. Previsivelmente, o único caso de insuficiência cardíaca foi reversível.[13]

No global, 13 de 88 doentes (14,8%) apresentaram diminuições assintomáticas a FeVE e 1 em 88 (7,1%) insuficiência cardíaca congestiva. Apesar das taxas mais baixas de suspensão ou adiamento de trastuzumab e diminuições assintomáticas, talvez devido ao tamanho inferior da amostra, estes resultados podem ser comparados às conclusões do estudo NSABP B-31 (de 31% de doentes avaliáveis que adiaram temporariamente ou suspenderam trastuzumab, 8% tinham toxicidade cardíaca sintomática e 24% diminuições assintomáticas da FeVE.[13]

A ausência de associações pode refletir o menor tamanho da amostra, que não permite ter poder estatístico, mas deve ser reforçado que a maioria destas doentes tratadas com estes esquemas são selecionadas pelo seu bom estado geral para suportar o tratamento com quimioterapia. Assim, não deve ser surpreendente que a maioria das doentes sejam relativamente jovens (a maioria entre os 40-65 anos), sem muitas comorbilidades e com bom *performance status* (ECOG 0 e 1).

Em conclusão, nesta série os eventos cardíacos foram pouco frequentes e a maioria das diminuições da FeVE foram assintomáticas. O único caso de insuficiência cardíaca congestiva reverteu após adiamento de tratamento. Como perspetivas futuras, o alargamento da série e a avaliação da toxicidade cardíaca a longo prazo seria relevante.