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ORIGINAL ARTICLE

Cardiotoxicity associated with trastuzumab in normal clinical practice

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Abstract
Objective: To evaluate the incidence of cardiotoxicity associated with treatment with trastuzumab in clinical practice by describing its characteristics, progress, and associated risk factors.
Methods: Retrospective observational study of patients with HER2-positive breast cancer treated with trastuzumab in the first quarter of 2007 in a tertiary hospital. Follow-up was performed from start of treatment until the end of March 2008. The data sources used were the oncological computer program Oncowin® from the pharmacy department and the patient clinical history. We gathered variables related to patient baseline characteristics, treatment, and safety.
Results: The study included 61 patients. 19 women (32.8%) presented cardiotoxicity, which was the second most common adverse affect of those frequently attributed to the treatment. The average time for toxicity to appear was 7 months, with an average FEVI decrease of 15.6 (9.1) points. In 63.2% of the patients it was symptomatic, and its most frequent manifestation was stress-induced dyspnoea, with a single case of congestive heart failure. Cardiotoxicity led to suspension of treatment in 22.9% of the total patients, which was definitive for 7 out of the 14 patients who interrupted the treatment. No statistically significant differences were found for the possible risk factors.
Conclusions: The incidence of cardiotoxicity in clinical practice is much higher than expected. The important clinical implication of this information and the increasing use of trastuzumab mean that there is a new challenge for the optimal treatment of HER2-positive breast cancer.

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PALABRAS CLAVE
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Trastuzumab;
Efectos adversos

Cardiotoxicidad asociada a trastuzumab en la práctica clínica asistencial

Resumen

Objetivo: Evaluar la incidencia de cardiotoxicidad asociada al tratamiento con trastuzumab en la práctica clínica asistencial, describiendo sus características, su manejo y los factores de riesgo asociados.

Método: Estudio observacional retrospectivo que incluyó a pacientes con cáncer de mama HER-2 positivo en tratamiento con trastuzumab durante el primer trimestre de 2007 en un hospital de tercer nivel. Se realizó un seguimiento desde el inicio del tratamiento hasta finales de marzo de 2008. Las fuentes de datos utilizadas fueron el programa informático de oncología del servicio de farmacia, Oncowin®, y la historia clínica del paciente. Se recogieron variables relacionadas con las características basales del paciente, con el tratamiento y con la seguridad.

Resultados: Se incluyó a 61 pacientes en el estudio; 19 (32,8 %) mujeres presentaron cardiotoxicidad, que supuso el segundo efecto adverso atribuido el tratamiento en frecuencia. La mediana de tiempo de aparición de la toxicidad fue de 7 meses, con un descenso medio de fracción de eyección del ventrículo izquierdo (FEVI) de 15,6 ± 9,1 puntos. En el 63,2 % fue sintomática, la manifestación más frecuente fue la disnea de esfuerzo y hubo un único caso de fallo cardíaco congestivo. La cardiotoxicidad supuso la suspensión del tratamiento en el 22,9% del total de pacientes, y fue de forma definitiva en 7 de las 14 pacientes que interrumpieron el tratamiento. No se hallaron diferencias estadísticamente significativas en cuanto a los posibles factores de riesgo.

Conclusiones: La incidencia de cardiotoxicidad en la práctica clínica asistencial se muestra mucho más elevada que la esperada. Su importante implicación clínica y el uso creciente de trastuzumab hacen que suponga un nuevo reto para el tratamiento óptimo del cáncer de mama HER-2 positivo.

Introduction

The appearance of trastuzumab revolutionised the treatment of breast cancer with HER-2 overexpression, which makes up about 15%-25% of all cases and had previously had a poor prognosis.[1-3] Its use is currently approved for the treatment of metastatic cancer that overexpresses HER-2, either as monotherapy or in combination with taxanes or aromatase inhibitors, and as an adjuvant treatment for early onset HER-2 breast cancer following surgery, chemotherapy, or radiation therapy.[4] Treatment is generally well-tolerated, with a low incidence rate of adverse effects[5]; the most relevant is cardiotoxicity, which appears in 2.6%-4.5% of the patients treated in monotherapy, in 27% of those on combined therapy with anthracyclines and 13% of those on combined therapy with paclitaxel.[6,7] It can manifest as asymptomatic decreases in left ventricular ejection fraction (LVEF) or symptomatically as congestive heart failure (CHF), which may cause death.[1]

The physiopathology of cardiac dysfunction associated with trastuzumab is unclear.[8] Advanced age and the concomitant use of anthracyclines seem to be significant predictive factors for cardiac dysfunction. Different studies have suggested that baseline LVEF, previous exposure to anthracyclines, time elapsed since the last treatment, previous radiation treatment in the thoracic wall and pre-existing cardiac dysfunction are all risk factors associated with cardiotoxicity. Cardiotoxicity associated with trastuzumab is not related to the dosage. In most cases, it is reversible and responds to discontinuing the drug and/or standard CHF treatment, which includes β-blockers, diuretics, and cardiotonic glycosides.[5] Recent data indicate that about 80% of patients may experience improved symptoms with this treatment.[9]

The use of trastuzumab in clinical care has exposed the perception that the cardiotoxicity incidence rate is higher than that shown by clinical trial data. In August 2006, the American press published the first alerts referring to a higher proportion of cardiac damage in patients with metastatic breast cancer.[10] Given the important role that trastuzumab currently plays in the treatment of HER-2 positive breast cancer and the clinical relevance of that toxicity, which could determine whether the treatment will be continued, therefore affecting patient evolution and prognosis, an assessment of trastuzumab's toxicity profile is needed. It would help us to make more rational use of this antineoplastic drug, maximise its effectiveness and minimise its toxicity.

The purpose of this study is to evaluate the cardiotoxicity incidence rate associated with trastuzumab treatment in clinical practice by describing its characteristics, its management and potential associated risk factors.

Method

This retrospective observational study included all women with HER-2 breast cancer undergoing treatment with

Table 1 Characteristics of patients included in the study (n=61)

Related to the disease	Related to the treatment
Tumour state at the start of trastuzumab treatment D1: 5.4% D2: 51.8% D3: 42.8%	Tumour state at the start of trastuzumab treatment I: 26.2% IIIa: 9.8% IIa: 18% IIIb: 4.9% IIb: 8.2% IV: 32.8%
Degree of HER-2 overexpression by immunohistochemistry Double positive: 26.2% Triple positive: 73.8%	Age at the start of trastuzumab treatment Mean (SD), y: 57.8 (11.2) Minimum–maximum value: 31-84
Hormone receptors Positives: 65.6% Negatives: 34.4%	Baseline LVEF Mean (SD), %: 63.0 (8.0) Minimum–maximum value: 48-78
Ganglion involvement Positives: 58.3% Negatives: 41.7%	Hormone therapy Yes: 70.5% No: 29.5%
Menopausal state Premenopausal: 32.8% Postmenopausal: 67.2%	Radiation therapy Yes: 86.9% No: 13.1%

LVEF indicates left ventricular ejection fraction; SD, standard deviation.

trastuzumab during the first quarter of 2007 in the oncological medicine division of a tertiary hospital. We excluded patients who began trastuzumab treatment as a neoadjuvant clinical trial (as the purpose was to evaluate cardiotoxicity in patients who were not pre-selected and whose treatment met the approved indications on the package leaflet), as well as those whose clinical history was unavailable or did not include oncological history information. Each patient was monitored from beginning trastuzumab treatment until March 31, 2008. Patients were selected from the Pharmacy Department's oncology database, OncoWin®. Each patient's clinical, evolution and treatment safety data was obtained by reviewing patients' clinical histories. We collected the variables related with the patient's baseline characteristics (age, tumour state and menopausal state at time treatment began, degree of tumour differentiation, ganglion involvement, hormone receptors, and degree of HER-2 positivity). Treatment data (duration, monotherapy or combination use, previous use of anthracyclines and time since the last dose, where applicable, radiation treatment, hormone therapy and concomitant treatment with taxanes) and safety data (LVEF evolution, symptomatic/asymptomatic cardiotoxicity, when it occurred, actions taken and evolution) were also gathered. The LVEF was recorded prior to beginning trastuzumab treatment, and once the treatment started it was measured on a quarterly basis during the first year of treatment, and annually thereafter. We also studied the influence of diverse factors considered to be predictive of the cardiotoxicity incidence rate, including age when treatment began, prior history of heart disease, hypercholesterolaemia, arterial hypertension, obesity, and hypothyroidism. The information was recorded in an Excel database and analysed with the statistics software SPSS, version 12.0. A logistical regression analysis was performed to examine which variables influence in whether or not a patient presents cardiotoxicity.

Results

Of the 89 patients who were treated during the study period, 13 were excluded due to their clinical histories being unavailable, and 15 were excluded for having started trastuzumab as a neoadjuvant treatment within a clinical trial; we present data from 61 patients. The baseline characteristics of the patients are shown in Table 1. It must be stated that before starting the trastuzumab treatment, 14.7% of the patients presented arterial hypertension and 8.2% presented heart disease.

Out of the patients who were studied, 65.6% (40 cases) began adjuvant treatment with trastuzumab following surgery and 34.4% (21 cases) began treatment for metastatic cancer. The average time of treatment with trastuzumab was 11.9 months, with durations ranging from 2 to 113 months. At the end of follow-up, 12 patients continued to receive trastuzumab, which was used to treat a metastatic condition in 11 of them. Forty-nine women were no longer receiving treatment at the end of the study. Of these patients, treatment was discontinued in 31 because they had completed the year of adjuvant therapy, treatment was discontinued in 8 due to progression of the disease, and in the remainder, due to adverse effects.

Forty-nine point two percent of the patients received trastuzumab as monotherapy, 45.9% alternated a period of monotherapy with a combination period, the most common combination was with taxanes, followed by vinorelbin, and the rest received trastuzumab in association with other drugs at all times (capecitabine, gemcitabine, or liposomal doxorubicin).

There were adverse effects in 49 patients (80.3%); the most frequent was the increase in middle to upper respiratory infections. Cardiotoxicity was the second most frequent effect. The most common adverse effects are listed in Figure. One patient abandoned treatment with

trastuzumab due to an adverse effect that was not cardiotoxicity. In this case the patient experienced intense flu-like syndromes, with headache, fever, arthromyalgia, and pharangitis which resolved after discontinuing the treatment and reappeared when the treatment was started again, which led to the definitive suspension of the trastuzumab.

Cardiotoxicity is defined as a LVEF decrease below normal values (50%) or an absolute decrease of >10 points below the baseline value. According to these criteria, 32.8%of the patients (19 women) presented cardiotoxicity. The number of patients who met each of these criteria is listed on Table 2, along with the number of patients who experienced a decrease of ≥15 points from the baseline value. The median time for the cardiotoxicity to appear was 7 months from beginning treatment (range, 4-78). The mean LVEF decrease in patients with cardiotoxicity was 15.6 (9.1) points from the baseline level (ranging, 4-37).

In 63.2%of the patients with cardiotoxicity (12 cases), the condition was symptomatic; in the remaining 36.8% (7 cases), there were asymptomatic decreases in the LVEF. The most commonly occurring symptom was exertion-induced dyspnoea. There was 1 case of CHF and there were no deaths due to cardiotoxicity (Table 3).

Of the 19 patients who presented cardiotoxicity, 14 (73.7%) had to discontinue treatment; this number constitutes 22.9%of the patient total. In 7 patients, treatment was resumed after normalising parameters, while in the other 7 it was suspended definitively; 3 of these cases received pharmacological treatment for heart failure.

In the patients who were studied, we observed that only 4 patients of the 14 who presented a LVEF decrease below 50%did not experience any cardiotoxicity improvement. In these patients, the LVEF values remained below normal and even reached levels as low as 28% Of the 5 patients who experienced a significant LVEF decrease from baseline levels, but whose value was within the normal range, values went back to normal levels in a relatively short time. This caused trastuzumab treatment to be discontinued in three patients, and in one, the suspension was permanent.

Twenty-six point three percent of the patients who used trastuzumab as adjuvant therapy presented cardiotoxicity, while 45.0%of those being treated for metastatic cancer, although the differences were not statistically significant (P=.15; χ^2).

When we analyse the influence of each separate predictive factor for cardiac dysfunction and the appearance of cardiotoxicity, we find no statistically significant differences for hypercholesterolaemia, prior heart disease, arterial hypertension, or obesity. We observed a tendency toward having a more advanced age at the time treatment was started in the patient group experiencing toxicity (58.2 [12.0] years vs 54.4 [11.4] years), although this was not statistically significant either (P=.255 by the Student t test. Out of the patient total, 10 had hypothyroidism, and out of these, half (5) developed cardiac dysfunction (P=.202 by the χ^2 test).

Almost three quarters of the patients with cardiotoxicity (14/19) had previously received treatment with anthracyclines, although this was not statistically significant (P=.366 by χ^2). Likewise, there were no differences observed for the cumulative dose (P=.9 in the Mann-Whitney U test), and in the elapsed time since those drugs were last administered and the start of trastuzumab treatment

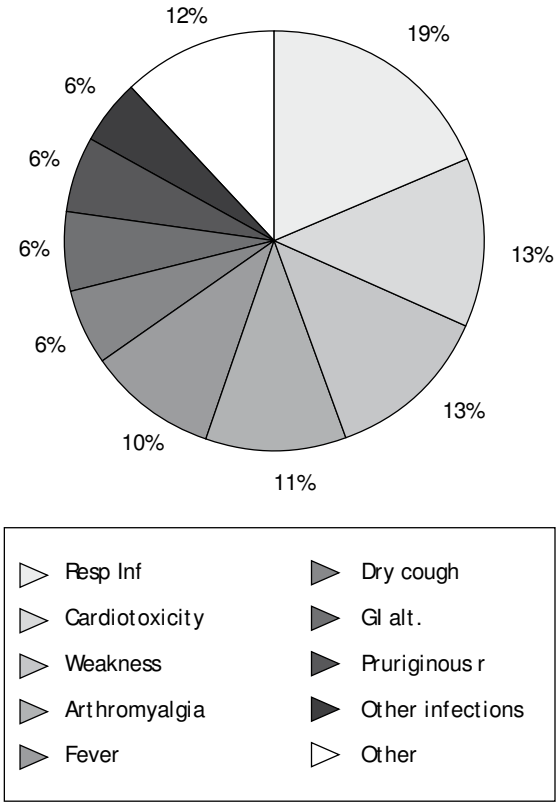

Figure Adverse effects attributed to trastuzumab treatment. GI alt indicates gastrointestinal alterations, such as diarrhoea and constipation; Others, include infusion reaction, dyspepsia, drowsiness, headache, flu-like syndrome, and fingernail alterations; Resp inf, middle-upper respiratory tract infection; Pruriginous r, pruriginous cutaneous reaction.

Table 2 Characteristics of the LVEF decrease in patients with cardiotoxicity (n=19)

Cardiotoxicity criteria	No. patients	Patients with cardiotoxicity, %	%of patient total
LVEF decrease <50%	15	78.9	24.6
LVEF decrease ≥10 points below baseline	14	73.7	23.0
LVEF decrease ≥15 points below baseline	10	52.6	16.4

LVEF indicates left ventricular ejection fraction.

Table 3 Cardiotoxicity symptoms shown by patients in the study

Symptoms	No. patients (%)
Dyspnoea	9 (47.4)
Dyspnoea with exertion	8 (42.1)
Oedemas in LE	4 (21.1)
Pleural effusion	2 (10.5)
Pericardial effusion	2 (10.5)
Dyspnoea at rest	1 (5.3)
Pulmonary hypertension	1 (5.3)
Tachycardia	1 (5.3)
Presyncopal episode	1 (5.3)
Congestive heart failure	1 (5.3)

LE indicates lower extremities.

(P=.588 in the Mann-Whitney U test). More than half of the patients with cardiotoxicity (13/19) had previously received treatment with taxanes or had received them concomitantly with the trastuzumab, but no statistical significance was found (P=.301 by the χ^2 test).

Radiation therapy was also not associated in a significant way with an increased cardiotoxicity incidence rate, although 57.9% of the affected patients (11/19) had received radiation, whether prior to or concomitantly with trastuzumab treatment (P=.647 by χ^2).

In the logistical regression analysis, there were no statistically significant results for any of the odds ration for the different variables that were analysed (age, pre-existing heart disease, arterial hypertension, hypercholesterolaemia, obesity, hypothyroidism, radiation treatment, previous anthracycline use, and concomitant treatment with taxanes).

Discussion

Trastuzumab is the standard drug for treating patients with breast cancer that overexpresses HER-2. In our study, the drug was used as an adjuvant monotherapy in nearly half of the cases, and its use in combination with other drugs was limited to the event of treating metastatic cancer.

Most of the patients who experienced an adverse effect associated with trastuzumab, but if we exclude cardiotoxicity, which was the second most common adverse effect, the rest were of a more moderate nature and only caused treatment to be suspended for 1 patient. Cardiotoxicity was initially described in women with metastatic breast cancer, with a higher incidence rate when trastuzumab was administered with anthracyclines.[7] Based on these data, the concomitant use of anthracyclines and trastuzumab was discouraged due to the greater risk of presenting cardiotoxicity. Subsequently, several adjuvant clinical trials reached CHF rates below 4%, which were considered acceptable.[6,11] However, the cardiotoxicity incidence rate in the population of women receiving treatment outside of clinical trials is unknown. It is normal to find references alluding to the difference between patients selected in clinical trials and those treated in a clinical care situation, and these differences may have an important effect on some treatments. In the HERA trial, one of the patient exclusion criteria was the presence of arterial hypertension or prior heart disease. Our study, however, included patients who had cardiac disease and/or arterial hypertension before beginning the treatment, and they were treated with trastuzumab; despite that fact, we found no significant differences in the appearance of cardiotoxicity in these patients. The cardiotoxicity incidence rate in our study was very high (32.8%) if we compare it to that obtained in adjuvant clinical trials.[6] In the HERA study,[12] the percentage of patients with at least a significant LVEF decrease, defined as a drop of 10 points or more from the baseline level, reaching less than 50%, was 7.4% in the trastuzumab group.[11] In a 1 year (minimum) follow-up study of normal clinical practice with patients with metastatic breast cancer, the global incidence rate of cardiac dysfunction was 28%, which is much more similar to the result obtained in our study.[13]

More than half of the patients presented symptomatic cardiotoxicity with moderate symptoms; in most patients, these were dyspnoea with moderate exertion and oedema of the lower extremities. The percentage of symptomatic patients was much higher than that obtained in the different clinical trials,[6,11] but most cases were not severe; the most noteworthy events were a presyncopal episode, 2 pleural effusions, 1 case of pulmonary hypertension, several cases of pericardial effusion, and a single case of CHF, all of which were attributed to the treatment. LVEF decrease below the normal limits will affect a considerable percentage of patients (more than 20%), although in some cases, the decrease was asymptomatic and had no clinical relevance.

In our study, 22.9% of the patients who were included had to suspend trastuzumab treatment, whether temporarily or definitively, due to cardiotoxicity. In the McArthur and Chia study,[14] the treatment has a 21.6% suspension rate due to cardiac dysfunction, which is much higher than the number reported in the HERA[15] clinical trial and closer to the rate shown by our patients. However, the same study shows that most of the patients who discontinued treatment were able to resume it after recovering their cardiac function; in our study, however, half of the patients who interrupted treatment ended up suspending it definitively. In 8.2% of the patients (5 cases), there were asymptomatic LVEF decreases of 10 or more points below the baseline level and within the normal range, and for whom treatment was not suspended due to the absence of clinical repercussions and to the recovery they demonstrated in subsequent assessments. Based on the results we obtained, we can point to the apparent reversibility of trastuzumab-induced cardiotoxicity, since only 4 patients did not improve and their LVEF remained low. This coincides with what we know as of today, based on results from numerous studies, about the characteristics of trastuzumab-associated cardiotoxicity.[9,16,17]

The bibliography section shows the different factors that are associated with a higher risk of developing cardiotoxicity during trastuzumab treatment. The most well-known independent risk factors are advanced age and previous exposure to anthracyclines.[18] In our case, patients who experienced toxicity have a slightly higher mean age than

those who did not, but the differences were not statistically significant. A similar effect occurred with prior use of anthracyclines; a higher cardiotoxicity incidence rate was not found for a larger cumulative dose. Other cardiovascular risk factors, such as hypertension, prior heart disease, hypercholesterolaemia and obesity are also described in the literature as predictive factors for developing trastuzumab-associated cardiotoxicity. In our study, however, no statistically significant differences were found, which may be due to the small sample size.[11,18,19]

As in the HERA[12] and the NCCTG N9831 studies,[20] prior or concomitant radiation therapy did not increase the incidence rate of cardiac dysfunction in our study; however, as the literature indicates, caution and close monitoring are advised because the possible consequences are not known.[18] In addition, the HERA study also observed a tendency toward a higher cardiotoxicity incidence rate in patients with non-metastatic breast cancer, which we did not observe in our study.[11]

The study's primary limitation was its low number of patients, which was too small for it to obtain significant results. Likewise, the follow-up time for the patients was varied and not vary long, which limits our ability to understand the long-term consequences of trastuzumab treatment. It is also important to consider that comparing cardiac safety among patients receiving treatment in a non-clinical trial setting is complicated, since patients who receive trastuzumab as a clinical care procedure cannot be compared to those selected for clinical trials, which have very strict exclusion criteria. Furthermore, the criteria used to describe cardiotoxicity vary from study to study, making comparisons difficult. For this reason, it will be necessary to carry out studies with a larger number of patients and over a longer period of time in order to obtain more reliable answers regarding long-term cardiac tolerance and consequences in clinical care.

Despite these limitations, the results we obtained coincide with published studies, in that trastuzumab-related cardiotoxicity in the clinical care setting is more frequent than is shown by clinical trial estimates. The increasingly early detection of breast cancer and the growing use of trastuzumab in patients with HER-2 overexpression, due to its good and effective results shown in clinical trials, have led to treatment beginning earlier. Its primarily adjuvant use and its possible application in neoadjuvant treatment, suggested by clinical trials currently in progress, mean that the clinical implications of the cardiotoxicity that these patients may develop are greater than in metastatic patients and those with very high mortality and morbidity, due to the former having a better life expectancy. All of these considerations lead us to consider the size of the problem posed by trastuzumab-induced cardiotoxicity, and how we can manage it. Proper monitoring of patients being treated with this monoclonal antibody, and establishing alert parameters for follow-up will allow us to foster safe use of trastuzumab in which the risk of cardiotoxicity does not outweigh its possible clinical benefits.

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