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Real world study of pertuzumab-trastuzumab-chemotherapy versus trastuzumab-chemotherapy in neoadjuvant treatment of breast cancer

Estudio en vida real de pertuzumab-trastuzumab-quimioterapia frente a trastuzumab-quimioterapia en neoadyuvancia en cáncer de mama

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Abstract

Objective: The primary objective of the study is to compare the effectiveness of trastuzumab-chemotherapy with and without pertuzumab. As a secondary objective, we seek to evaluate the cardiac safety of the treatment.

Method: Retrospective observational study including all patients treated with either pertuzumab-trastuzumab-chemotherapy (*n* = 10) or trastuzumab-chemotherapy (*n* = 13) (January 2015-December 2018) in a specialty hospital, which met the criteria established by the Commission Central for the Optimization and Harmonization of the pharmacotherapy of the Andalusian Health Service for the use of pertuzumab in neoadjuvance: HER2 positive tumor, negative hormonal receptors, with high risk of relapse (tumor > 2 cm or lymph node involvement). To assess effectiveness, the complete pathological response was used. For cardiac safety, the decrease in left ventricular ejection fraction greater than 10% was employed.

Results: Complete pathological response was superior in the pertuzumab group (70.0% vs. 30.8%). Cardiac safety was similar in both.

Conclusions: For patients with HER2 positive tumors and negative hormonal receptors with high risk criteria that receive pertuzumab, the complete pathological response is superior, with no increase in cardiac toxicity.

KEYWORDS
Pertuzumab; Trastuzumab; Pathological complete response; Breast cancer; Neoadjuvance.

Resumen

Objetivo: El objetivo primario del estudio es comparar la efectividad de trastuzumab-quimioterapia con y sin pertuzumab. Como objetivo secundario se busca evaluar la seguridad cardiaca del tratamiento.

Método: Estudio observacional retrospectivo que incluyó todas las pacientes tratadas con pertuzumab-trastuzumab-quimioterapia (*n* = 10) o trastuzumab-quimioterapia (*n* = 13) (enero 2015-diciembre 2018) en un hospital de especialidades, que cumplían los criterios establecidos por la Comisión Central para la Optimización y Armonización de la farmacoterapia del Servicio Andaluz de Salud para uso de pertuzumab en neoadyuvancia: tumor HER2 positivo, receptores hormonales negativos, con alto riesgo de recaída (tumor > 2 cm o afectación ganglionar). Para valorar la efectividad se utilizó la respuesta completa patológica, y para la seguridad cardiaca, el descenso de la fracción de eyección del ventrículo izquierdo superior al 10%.

Resultados: La respuesta completa patológica fue superior en el grupo con pertuzumab (70,0% *versus* 30,8%). La seguridad cardiaca fue similar en ambos.

Conclusiones: Para las pacientes con tumores HER2 positivo y receptores hormonales negativos con criterios de alto riesgo que reciben pertuzumab, la respuesta completa patológica resulta superior, sin observarse incremento de la toxicidad cardiaca.

PALABRAS CLAVE
Pertuzumab; Trastuzumab; Respuesta completa patológica; Cáncer de mama; Neoadyuvancia.

Introduction

In Spain, breast cancer is the second most diagnosed type of cancer, with a 5-year prevalence of 129,928 patients (GLOBOCAN 2018[1]).

In most cases, it is diagnosed in localized stages, and adjuvant/neoadjuvant complementary chemotherapeutic treatment is indicated, both presenting similar efficacy in terms of disease-free survival (DFS) and overall survival (OS). Neoadjuvant therapy has added advantages, such as allowing higher rates of conservative breast surgery[2].

In 20-25% of cases, the tumor overexpresses HER2 receptors, being a factor of poor prognosis[3]. In recent years, trastuzumab + chemotherapy (T-CT) has been considered to be the treatment of choice in these tumors[4]. Pertuzumab, like trastuzumab, is an anti-HER2 monoclonal antibody, which acts on a different subdomain to that used by trastuzumab, both of which are complementary in the tumor cell's receptor blockade. Pertuzumab in neoadjuvant therapy is indicated together with trastuzumab + chemotherapy (PT-QT) in locally advanced HER2 positive breast cancer, inflammatory or at an early stage with a high risk of relapse[5].

To evaluate the efficacy of pertuzumab in neoadjuvant therapy, two phase II trials were performed: NeoSphere and Tryphaena. The first evaluated different combinations of pertuzumab and trastuzumab with docetaxel, the main variable being the complete pathological response (pCR). A higher pCR was observed with pertuzumab-trastuzumab-docetaxel (group B), and also a greater benefit in those patients who did not express hormonal receptors (HR)[6]. The Tryphaena[7] trial evaluated cardiac safety and efficacy of various neoadjuvant treatment regimens including pertuzumab and trastuzumab.

The use of the pCR in both trials was allowed by the European Medicines Agency (EMA) due to the correlation observed with DFS and OS, but not being validated as a surrogate survival variable[8,9], so the EMA requested a confirmatory trial: Aphinity[10]; which included adjuvant patients and used invasive disease-free survival (IDFS) as the main variable. In this trial, a subgroup analysis was performed according to lymph node involvement and only statistically significant differences were observed in patients with positive nodes.

Under this assumption, the Central Commission for Pharmacotherapeutic Optimization and Harmonization (CCOAFT by its Spanish acronym) of the Andalusian Health Service established as a necessary condition for the use of pertuzumab in neoadjuvant patients to have negative HER2 positive RH tumor with high risk of relapse, being tumor defined as > 2 cm or lymph node involvement[11].

The main objective of this study is to evaluate and compare the effectiveness results of neoadjuvant treatment with T-CT with/without pertuzumab. As a secondary objective, we seek to evaluate the cardiac safety of the treatment.

Methods

This is a retrospective observational study that included all patients with HER2 positive RH negative breast cancer who received neoadjuvant treatment (January 2015-December 2018) in a specialty hospital and who met the CCOAFT criteria for high risk of relapse: tumor > 2 cm or lymph node involvement. Two groups of patients were differentiated according to the treatment received: T-CT (trastuzumab + docetaxel-carboplatin, epirubicin-cyclophosphamide + docetaxel or others of equivalent efficacy) or PT-CT (PT-docetaxel-carboplatin).

Descriptive variables (age, tumor size, Ki67, histological grade, lymph node involvement and neoadjuvant treatment) and clinical variables (effectiveness/safety) were collected. To measure effectiveness, the pCR was used after neoadjuvant (defining pCR as the total absence of neoplastic cells in breasts and armpits, according to the Symmans criteria[12]; equivalent to grade 5 in the Miller and Payne classification). Regarding safety, the appearance of a decrease in the left ventricular ejection fraction (LVEF) > 10% was considered after neoadjuvance.

Data were collected from the Farmis-Oncofarm® chemotherapy prescription program and the electronic medical record available at the hospital, both later processed using Microsoft Excel®.

The study was approved by the Ethical Committee of the Southern Health Management Area of Seville.

Results

Thirteen patients were included in the T-CT group and ten in the PT-CT group, whose baseline characteristics are shown in table 1.

The percentage of patients who achieved pCR was 70.0% in the PT-CT group versus 30.8% in the T-CT group. Table 2 shows the pCR according to the high risk criteria presented by the patients.

There were two cases of LVEF > 10% descent in the T-CT group and one in the PT-CT group (16.7% versus 10.0%), but no patient reached LVEF < 45% (although post-chemotherapy LVEF values were reached by 48% in a patient belonging to the T-CT group, and 45% in a patient of the PT-CT group).

Discussion

As far as the authors know, three real-life studies of pertuzumab in neoadjuvance have been published[13-15], but this is the first study to have selected the patients who could benefit most from the use of the drug (according to CCOAFT criteria). It is interesting to confirm whether these selection criteria –chosen on the basis of the results obtained in the pivotal trials of pertuzumab in neoadjuvant therapy– imply an improvement in the effectiveness of the therapies in the routine clinical practice.

In this study, the percentage of patients who achieved pCR is much higher in the group that received pertuzumab. In addition, the pCR rate in this group was higher than that observed in the pivotal pertuzumab trials in neoadjuvance: Out of group B patients, it was found 32.7% of pCR in breast and armpit in the NeoSphere trial (PT-docetaxel), while for arm C, an amount of 51.9% in the Tryphaena trial was identified (PT-docetaxel-

Table 1. Baseline characteristics of the patients

Variable	PT-CT group (*n* = 10)	T-CT group (*n* = 13)
Median age, years (rank)	48.9 (33.0-72.0)	52.0 (30.0-76.0)
Median size, cm (range)	2.4 (0.8-9.8)	2.7 (1.7-10.0)
Ki67 median, % (range)	54.0 (30.0-80.0)	60.0 (20.0-80.0)
Nottingham histological grade, *n* (%)		
– Grade 2	2 (20.0%)	5 (38.5%)
– Grade 3	8 (80.0%)	8 (61.5%)
Lymph node involvement, *n* (%)		
– Yes	6 (60.0%)	7 (53.9%)
– No	4 (40.0%)	6 (46.1%)
Chemotherapeutic treatment received, *n* (%)		
– Docetaxel-carboplatin x 6	10 (100%)	4 (30.8%)
– Epirubicin-cyclophosphamide x 4 + docetaxel x 4	0 (0%)	8 (61.5%)
– Others	0 (0%)	1 (7.7%)

PT-CT: pertuzumab-trastuzumab-chemotherapy; T-CT: trastuzumab-chemotherapy.

Table 2. Pathological complete response based on the patients' high risk criteria

PT-CT group (*n* = 10)		T-CT group (*n* = 13)	
Overall pCR rate, *n* (%)	7 (70.0%)	Overall pCR rate, *n* (%)	4 (30.8%)
Risk criteria (*n*)	pCR, *n* (%)	Risk criteria (*n*)	pCR, *n* (%)
Lymph node involvement		Lymph node involvement	
Yes (*n* = 6)	6 (83.3%)	Yes (*n* = 7)	3 (42.8%)
No (*n* = 4)	2 (50.0%)	No (*n* = 6)	1 (16.7%)
Tumor size		Tumor size	
> 2 cm (*n* = 7)	5 (71.4%)	> 2 cm (*n* = 11)	4 (36.4%)
≤ 2 cm (*n* = 3)	2 (66.7%)	≤ 2 cm (*n* = 2)	0 (0.0%)
Lymph node involvement and tumor size > 2 cm (*n* = 4)	3 (75.0%)	Lymph node involvement and tumor size > 2 cm (*n* = 5)	3 (60.0%)

pCR: pathological complete response; PT-CT: pertuzumab-trastuzumab-chemotherapy; T-CT: trastuzumab-pertuzumab-chemotherapy.

carboplatin; a scheme received by patients in this study). Regarding the subgroup of negative RH patients from NeoSphere B arm, it is shown, however, a pCR rate of 63.2%, which is more similar to that observed in this real-life study (70.0%) for the PT-CT group, where all patients presented negative HR, as it was an inclusion criterion. Other real life studies show lower pCR rates for neoadjuvant pertuzumab than that observed in this study (52.8%[13] and 59.0%[14]), and are also more similar to those of the pivotal trials. These differences may also be due to a less strict patient selection.

The approval of pertuzumab in neoadjuvance by the EMA was conditional upon the verification of its efficacy with a confirmatory trial, as the pCR is not validated as a surrogate of survival variable[9]. The confirmatory trial[10] performs a pre-specified subgroup analysis according to lymph node involvement, with significantly higher IDFS being observed with pertuzumab, only in patients with positive nodes. In this study, the RCp in the PT-CT group was also higher among patients with lymph node involvement.

Regarding cardiac safety, 3.9% of patients in the C arm of the Tryphaena trial presented a LVEF > 10% decrease with LVEF < 50% post-chemotherapy. In this study, although some patients presented LVEF > 10% decreases and two reached a final < 50% value, in neither case < 45% values were reached, which would require the temporary interruption of anti-HER2 adjuvance treatment[5].

In addition, regarding the Tryphaena trial, cardiac safety is similar in all three arms (although they receive different chemotherapy schemes with/without anthracyclines). In this study, all patients whom LVEF > 10% decreased were treated without anthracyclines, so that toxicity could be attributed to antiHER2 treatment.

The main limitation of the study is the small sample size. In addition, only 30.8% of patients of the T-CT group received chemotherapy treatment with docetaxel-carboplatin, equal to that received by all patients in the PT-CT group. Although the remaining patients of the T-CT group received other equivalent clinical practice schemes in terms of effectiveness according to treatment guidelines, most patients received anthracyclines (and none in the PT-CT group), where cardiac safety outcomes for both groups could be less comparable.

In conclusion, taking into account the above limitations, pCR in patients with positive HER2 RH negative breast cancer with high risk criteria (tumor > 2 cm or positive nodes) treated with PT-CT in neoadjuvance is superior to that observed in T-CT, where pertuzumab addition does not imply that cardiac toxicity would increase. It would be interesting to prolong the follow-up in order to confirm whether pertuzumab is also an advantage in terms of survival.

Funding

No funding.

Conflict of interest

No conflict of interests.

Contribution to scientific literature

Pertuzumab is indicated in neoadjuvance for HER2 positive breast cancer, based on the results of phase II trials that used the pCR as an efficacy variable, considered valid for neoadjuvant studies, but whose correlation with the validated variables of long-term efficacy in this scope has not been fully demonstrated. Studies of the use of medicines in real life help us to confirm the external validity of the clinical trials outcomes.

We consider that this work is relevant for providing information on the effectiveness of the treatments used in routine clinical practice (with/without pertuzumab) and, especially, for having included patients who are supposed to have a greater benefit associated with pertuzumab (to be selected according to strict criteria). There are currently few real-life studies on pertuzumab in neoadjuvant and, as far as the authors know, none that have selected the patients this way.

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