

Adjuvant regimens with trastuzumab administered for small HER2-positive breast cancer in routine clinical practice

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Abstract

Purpose Trastuzumab has proven to improve the prognosis of HER2-positive breast cancer, but the information available about its administration for small tumors is still limited. Therefore, we assessed the use of adjuvant regimens with trastuzumab for the treatment of small HER2-positive breast cancer in routine clinical practice.

Methods This observational study was conducted in patients with HER2-positive breast adenocarcinoma ≤ 1.5 cm who received trastuzumab-based adjuvant treatment in clinical practice. Clinical/histopathological data were retrieved from patients' medical charts. **Results** A total of 101 evaluable patients were enrolled (median age [range], 56.7 [49.0–64.8] years; ECOG 0, 98.0 %; ductal carcinoma, 88.1 %; lymph nodes N0, 79.2 %). Only five (5.0 %) patients received neoadjuvant treatment, while all patients underwent tumor surgery. Adjuvant trastuzumab was administered at a mean ($\pm$ SD) dose of 5.9 ± 1.5 mg/kg/cycle, and mostly in a three-weekly schedule (89 [89.0 %] patients). The most frequent adjuvant therapy used with trastuzumab was chemotherapy (87 [86.1 %] patients), followed by radiotherapy (63 [62.4 %] patients) and hormone therapy (52 [51.5 %] patients). Chemotherapy regimens mainly included doxorubicin, cyclophosphamide and paclitaxel/docetaxel ($n = 30$), docetaxel and cyclophosphamide ($n = 15$), docetaxel and carboplatin ($n = 13$). Hormone therapy mainly included letrozole ($n = 17$) and tamoxifen ($n = 17$). Nine (8.9 %) patients reported trastuzumab-related adverse events; only one allergic reaction reached grade 3 toxicity.

Conclusion This study shows that trastuzumab-based adjuvant treatment of small HER2-positive breast cancer is mostly based on chemotherapy—mainly paclitaxel/docetaxel. Adjuvant administration of trastuzumab for small HER2-positive breast cancer seems to be similar to that used for larger tumors.

Keywords Adjuvant · Clinical practice · HER2-positive · Small breast cancer · Trastuzumab

On behalf of the SmallHER Study Group.

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Introduction

Diagnosis of small breast adenocarcinomas is increasing as a result of the widespread implementation of mammographic screening programs [1–3]. Even though small breast tumors have usually been considered to be low risk, their prognosis worsens when they overexpress the HER2/neu gene. In fact, HER2 overexpression has shown to represent a powerful adverse prognostic factor for patients with tumors even smaller than 1–2 cm [4, 5].

Trastuzumab is a humanized monoclonal antibody specifically designed to target the HER2 receptor, whose administration to patients with early HER2-positive breast cancer has consistently been reported to improve the prognosis of the disease in several clinical trials [6–10]. Although these clinical trials mainly included patients with large tumors, data obtained from those trials that allowed the inclusion of patients with tumor sizes ≤ 2 cm also supported the benefit of adding trastuzumab to adjuvant treatments [8, 9]. Furthermore, other observational studies focusing on patients with small HER2-positive breast cancers also supported such a benefit, as they reported significant improvements in terms of tumor recurrence and/or patient survival after the administration of adjuvant trastuzumab [11–14].

Both the St. Gallen's International Expert Consensus on the Primary Therapy of Early Breast Cancer and the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant therapy for T1bN0 patients [15, 16], and the European Society for Medical Oncology (ESMO) Clinical Practice guidelines state that adjuvant trastuzumab should be considered in the population with N0 tumors < 1 cm [17]. However, the final decision on administering trastuzumab and selection of the specific treatment regimens available in clinical practice lay with the physicians, who need to tailor the treatment to numerous patient and tumor characteristics. Therefore, further assessment of the adjuvant regimens used for small HER2-positive breast cancer in routine clinical practice would provide useful information to guide clinical decision-making.

In light of the above, this study aimed to expand the information available on the administration of adjuvant therapies with trastuzumab for the treatment of small HER2-positive breast cancer in clinical practice conditions.

Patients and methods

This study was conducted in accordance with the World Medical Association Declaration of Helsinki, all its amendments, and national regulations. The study was approved by the Clinical Research Ethic Committee of

Galicia (Santiago de Compostela, Spain) and all patients gave their informed consent before study enrollment.

Patient population

The study population consisted of patients aged ≥ 18 years, with histologically or cytologically confirmed primary breast adenocarcinoma, a tumor size of ≤ 1.5 cm, and overexpression or amplification of the HER2/neu gene by immunohistochemistry and/or in situ hybridization. Patients must have received or be receiving adjuvant anti-HER2 treatment with trastuzumab (Herceptin®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) under clinical practice conditions and have a left-ventricular ejection fraction ≥ 55 %. Additionally, the maximum cumulative dose of doxorubicin had to be > 360 mg/m² and the maximum cumulative dose of epirubicin > 720 mg/m² or equivalent. Patients participating in any clinical trial were excluded from the study.

Study design and assessments

This was a multicenter, cross-sectional, observational study conducted in the Departments of Oncology at 27 Spanish hospitals.

Patients' information was retrieved from their medical charts at a single study visit, which included demographics, body measurements, previous medical history/comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, and data related to breast cancer, tumor surgery (if any) and treatment (neoadjuvant and adjuvant therapies).

All treatments were administered according to routine clinical practice and no restrictions regarding patients' treatment were specified in the study protocol.

Statistical considerations

The primary endpoint comprised the adjuvant regimens with trastuzumab used for small HER2-positive breast cancer in routine clinical practice, which was analyzed using descriptive statistics: measures of central tendency and dispersion (mean and standard deviation [SD], or median and interquartile range) for quantitative variables, and frequency distribution (absolute frequencies and valid percentages) for qualitative variables. Sample size was calculated to fulfill the primary study objective, allowing the detection of treatment regimens received by at least 10 % of patients. Based on an annual incidence of breast cancer of 15,979 patients [18], a proportion of 30 % of patients with non-palpable tumor [19] and considering the principle of maximum variance for patients receiving anti-

HER2 treatment, it was estimated a total of 3538 patients with non-palpable breast cancer who may be receiving trastuzumab in Spain. Taking into account these figures, a precision of $\pm 6.5\%$, a type I error of 0.05 in a two-sided analysis and a percentage of missing data $\leq 10\%$, the estimated sample size was of 89 patients.

Secondary endpoints included the description of patients' biological profile and the comparison of adjuvant regimens with trastuzumab used in patients aged >70 years and ≤ 70 years. Analyses of these secondary endpoints consisted of descriptive statistics and comparisons carried out using Fisher's exact tests.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Between September 2011 and April 2012, a total of 103 patients were consecutively enrolled into the study. Two patients were not evaluable because their tumor sizes were larger than 1.5 cm. Therefore, the evaluable population finally comprised 101 patients, whose characteristics are described in Table 1.

Neoadjuvant therapy was only administered to five (5.0 %) patients, which consisted of chemotherapy and trastuzumab in all cases: doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab ($n = 2$); fluorouracil, epirubicin, cyclophosphamide and trastuzumab followed by docetaxel/paclitaxel and trastuzumab ($n = 2$); and docetaxel, carboplatin and trastuzumab ($n = 1$). Patients received a mean ($\pm$ SD) of 6.8 ± 1.8 cycles of chemotherapy and 4.0 ± 1.4 cycles of trastuzumab, which was administered three-weekly in all cases ($n = 5$). Neither radiotherapy nor hormone therapy were administered as neoadjuvant treatment. Data regarding the response to neoadjuvant treatment were available in four patients, which showed complete response in three patients and non-evaluable response in another.

All patients underwent surgery for tumor resection: tumorectomy ($n = 56$), mastectomy ($n = 24$), quadrantectomy ($n = 17$), segmentectomy ($n = 1$) and others ($n = 3$). Forty-six (45.5 %) patients had lymph nodes removed: axillary lymph nodes ($n = 36$), sentinel lymph nodes ($n = 9$) and internal mammary lymph nodes ($n = 1$). Among patients who underwent mastectomy, radical mastectomy was performed in 18 (78.3 %) patients.

Table 1 Patient characteristics ($N = 101$)

Patient characteristics	Value
Age (years)	
Median (IQR)	56.7 (49.0–64.8)
Age <70 years, n (%)	89 (88.1)
Caucasian, n (%)	100 (99.0)
Weight (kg), mean $\pm$ SD	66.6 $\pm$ 11.7
Body surface area (m^2), mean $\pm$ SD ^a	1.7 $\pm$ 0.2
Postmenopausal, n (%)	67 (66.3)
ECOG performance status, n (%)	
ECOG 0	99 (98.0)
ECOG 1	2 (2.0)
Family history of breast cancer, n (%)	12 (11.9)
Histopathologic type, n (%)	
Ductal carcinoma	89 (88.1)
Lobular carcinoma	5 (5.0)
Other	7 (6.9)
Tumor stage, n (%)	
Stage 0	1 (1.0)
Stage IA	79 (78.2)
Stage IIA	15 (14.9)
Stage IIIA	4 (4.0)
Stage IIIC	1 (1.0)
Non-assessable	1 (1.0)
Lymph node affectation, n (%)	
Nx	1 (1.0)
N0	80 (79.2)
N1	15 (14.9)
N2	4 (4.0)
N3	1 (1.0)
HER2-overexpression, n (%)	
IHC 2+	16 (15.8)
IHC 3+	85 (84.2)
FISH positive	38 (37.6)
CISH positive	6 (5.9)
Hormone receptors, n (%)	
ER positive ^a	69 (69.0)
PR positive	56 (55.4)
ER and/or PR positive	71 (70.3)
Tumor biomarkers, n (%)	
Ki67 positive ^b	78 (87.6)
p53 positive ^c	16 (32.7)
CA 15-3 positive ^d	5 (9.3)

CISH chromogenic in situ hybridization, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *FISH* fluorescent in situ hybridization, *IHC* immunohistochemistry, *IQR* interquartile range, *PR* progesterone receptor, *SD* standard deviation

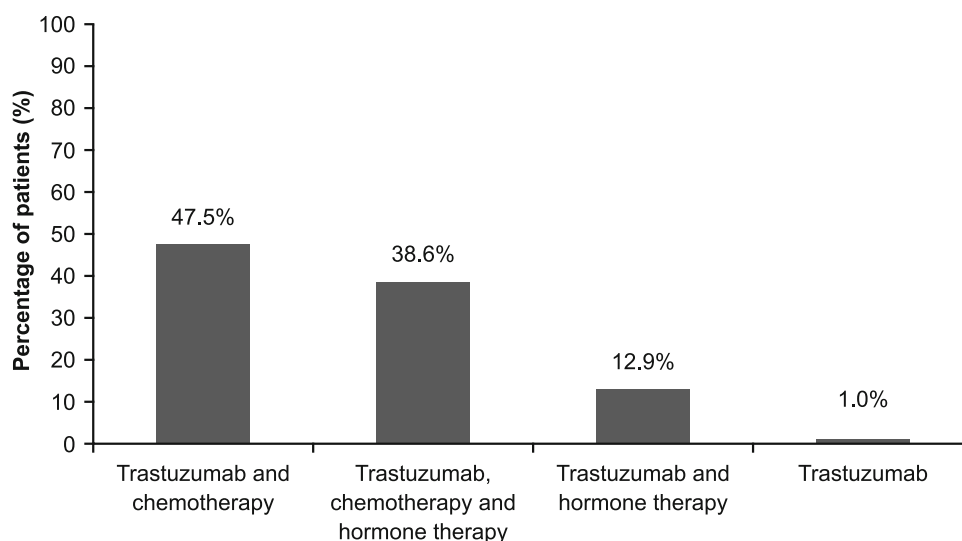
^a Missing data, $n = 1$

^b Missing data, $n = 12$

^c Missing data, $n = 52$

^d Missing data, $n = 47$

Fig. 1 Patient distribution according to adjuvant treatments with trastuzumab ($N = 101$)



Adjuvant therapy

The distribution and characteristics of adjuvant therapies with trastuzumab are summarized in Fig. 1 and Table 2. The most frequent adjuvant therapy used with trastuzumab was chemotherapy (87 [86.1 %] patients), followed by radiotherapy (63 [62.4 %] patients) and hormone therapy (52 [51.5 %] patients). A total of 19 patients with positive estrogen and/or progesterone receptors did not report having received adjuvant hormone therapy, most of whom were still under treatment with chemotherapy ($n = 11$); in the remaining patients, there was no information about the reasons for not having received hormone therapy ($n = 5$) or data on hormone therapy was missing ($n = 3$). Chemotherapy regimens mainly consisted of doxorubicin and cyclophosphamide followed by paclitaxel/docetaxel ($n = 30$), docetaxel and cyclophosphamide ($n = 15$), and docetaxel and carboplatin ($n = 13$). Hormone therapy regimens mostly included the administration of letrozole ($n = 17$) and tamoxifen ($n = 17$).

Trastuzumab was administered at a mean ($\pm$ SD) dose of 5.9 ± 1.5 mg/kg/cycle for a mean ($\pm$ SD) of 9.3 ± 6.3 cycles (Table 3). Eighty-nine (89.0 %) patients received trastuzumab in a three-weekly schedule, while 11 (11.0 %) patients received it in a weekly schedule. A total of seven (7.1 %) patients required trastuzumab modifications: six (6.0 %) patients due to investigator decisions unrelated to treatment toxicity and another (1.0 %) due to decreased left ventricular ejection fraction (Table 3). At the study visit, 25 (24.8 %) patients had finished treatment with trastuzumab, after having received a mean ($\pm$ SD) of 14.8 ± 4.4 cycles, while 76 (75.2 %) patients still remained on treatment. No disease recurrence was reported during adjuvant treatment with trastuzumab.

When the adjuvant therapy was compared between patients aged ≥ 70 years and < 70 years, no statistically significant differences were reported in terms of radiotherapy or hormone therapy administration. All patients received trastuzumab irrespective of their age and chemotherapy tended to be more frequently administered to patients aged < 70 years than to those aged ≥ 70 years (79 [88.8 %] patients versus 8 [66.7 %] patients; $p = 0.060$); no statistically significant differences were shown between the chemotherapy regimens used.

Safety

The addition of trastuzumab to the adjuvant therapy was well tolerated. Indeed, only nine (8.9 %) patients reported trastuzumab-related adverse events. All trastuzumab-related adverse events are shown in Table 4. Most adverse events were mild and only one patient suffered a grade 3 allergic reaction. No grade 4 toxicity was reported during trastuzumab treatment and no toxic deaths occurred due to trastuzumab therapy.

Discussion

The present observational study expands the information available on trastuzumab-based adjuvant therapies used in routine clinical practice for small HER2-positive breast cancers. The data from the evaluated sample showed that the administration of adjuvant trastuzumab for these cancers mostly involved chemotherapy administration, which mainly included doxorubicin and cyclophosphamide followed by paclitaxel/docetaxel, docetaxel and cyclophosphamide or docetaxel and carboplatin. Less frequent

Table 2 Characteristics of adjuvant therapies with trastuzumab ($N = 101$)

Treatment characteristics	Value
Chemotherapy ^a	
Patients receiving chemotherapy, n (%)	87 (86.1)
Number of cycles, mean $\pm$ SD	6.6 $\pm$ 4.1
Chemotherapy regimens, n (%)	
Doxorubicin and cyclophosphamide followed by paclitaxel	18 (17.8)
Docetaxel and cyclophosphamide	15 (14.9)
Docetaxel and carboplatin	13 (12.9)
Doxorubicin and cyclophosphamide followed by docetaxel	9 (8.9)
Fluorouracil, epirubicin and cyclophosphamide	7 (6.9)
Doxorubicin and cyclophosphamide	7 (6.9)
Fluorouracil, epirubicin, cyclophosphamide and paclitaxel	4 (4.0)
Docetaxel	4 (4.0)
Doxorubicin and cyclophosphamide followed by paclitaxel and docetaxel	3 (3.0)
Cyclophosphamide, methotrexate and fluorouracil	2 (2.0)
Fluorouracil, doxorubicin, cyclophosphamide and paclitaxel	1 (1.0)
Fluorouracil, epirubicin, cyclophosphamide and docetaxel	1 (1.0)
Docetaxel and vinorelbine	1 (1.0)
Docetaxel and doxorubicin	1 (1.0)
Paclitaxel	1 (1.0)
Radiotherapy ^a	
Patients receiving radiotherapy, n (%)	63 (62.4)
Total dose (Gy), mean $\pm$ SD ^b	50.4 $\pm$ 9.9
Hormone therapy: ^a	
Patients receiving hormone therapy, n (%)	52 (51.5)
Hormone therapy regimens, n (%):	
Letrozole	17 (16.8)
Tamoxifen	17 (16.8)
Anastrozole	8 (7.9)
Exemestane	6 (5.9)
Letrozole and exemestane	2 (2.0)
Letrozole, anastrozole and exemestane	1 (1.0)
Tamoxifen and goserelin	1 (1.0)

SD standard deviation

^a Patients may have received more than one of these therapies^b Missing data, $n = 10$

combinations with trastuzumab included its administration together with hormone therapies, mostly letrozole and tamoxifen. Radiotherapy was also administered according to clinical practice.

These results are in line with previous observational studies which also reported the predominant use of adjuvant trastuzumab together with chemotherapy for HER2-positive tumors smaller than 1–2 cm, reaching between 93 and 100 % of patients receiving trastuzumab-based therapies [12–14]. The specific regimens used in combination with trastuzumab for small tumors are not consistently described and are therefore poorly established. The information available suggests an unclear

scenario, in which a single-institution retrospective study reported the main use of trastuzumab within chemotherapy regimens based on anthracyclines with taxanes, followed by taxanes without anthracyclines and anthracyclines without taxanes [12]. A recent multicenter retrospective study coincides in reporting anthracyclines with taxanes as the main trastuzumab-based adjuvant chemotherapy, but followed by anthracyclines alone and taxane-only regimens [14]. However, another multicenter retrospective study found anthracyclines without taxanes as the main chemotherapy choice, followed by anthracyclines with taxanes, taxanes only and finally anthracyclines alone [20].

Table 3 Characteristics of adjuvant trastuzumab administration ($N = 101$)

Characteristics of trastuzumab administration	Value
Dose (mg/kg), mean $\pm$ SD	5.9 $\pm$ 1.5
Number of cycles, mean $\pm$ SD ^a	9.3 $\pm$ 6.3
Administration schedule, n (%) ^b	
Three-weekly	89 (89.0)
Weekly	11 (11.0)
Treatment modifications ^c	
Patients with treatment modifications, n (%)	7 (7.1)
Reasons for treatment modifications, n (%):	
Investigator's decision unrelated to treatment toxicity	6 (6.0)
Decreased left ventricular ejection fraction	1 (1.0)
Patients who completed treatment	
Patients completing the planned treatment, n (%)	25 (24.8)
Number of cycles, mean $\pm$ SD ^c	14.8 $\pm$ 4.4
Patients who still remained on treatment, n (%)	76 (75.2)

SD standard deviation

^a Missing data, $n = 9$ ^b Missing data, $n = 1$ ^c Missing data, $n = 2$ **Table 4** Trastuzumab-related adverse events ($N = 101$)

Adverse event	All grades	Grade 3
Cardiac toxicity, n (%)	3 (3.0)	0 (0.0)
Mucositis, n (%)	2 (2.0)	0 (0.0)
Infusion reaction, n (%)	2 (2.0)	0 (0.0)
Allergic reaction, n (%)	2 (2.0)	1 (1.0)
Asthenia, n (%)	1 (1.0)	0 (0.0)
Conjunctivitis, n (%)	1 (1.0)	0 (0.0)
Acneiform facial eruption, n (%)	1 (1.0)	0 (0.0)
Folliculitis, n (%)	1 (1.0)	0 (0.0)
Bone discomfort, n (%)	1 (1.0)	0 (0.0)
Hematologic toxicity, n (%)	1 (1.0)	0 (0.0)

Unfortunately, to our knowledge, no randomized clinical trials assessing the efficacy of different trastuzumab-based adjuvant treatments for small HER2-positive breast cancers have been conducted yet. However, trastuzumab has proven its efficacy for larger HER2-positive tumors in the adjuvant setting in several trials when used within regimens containing anthracyclines and taxanes, anthracyclines without taxanes, taxanes without anthracyclines, and with hormone therapy such as tamoxifen or aromatase inhibitors [6–10, 21, 22]. The regimens described in these trials were similar to those observed in our study—mostly based on the administration of trastuzumab with paclitaxel or docetaxel following doxorubicin and cyclophosphamide

[6, 9, 21–23]—which led us to consider that adjuvant regimens with proven efficacy for larger breast cancer are also used for smaller tumors in the clinical practice setting. Indeed, a recently published single-arm clinical trial supported the benefit of administering adjuvant trastuzumab and paclitaxel for 12 weeks, followed by 9 months of trastuzumab monotherapy, for stage I HER2-positive tumors <3 cm, showing patient outcomes even better than expected from historical data [24].

Our safety data shows that the addition of trastuzumab to the adjuvant therapy was well tolerated—though many patients still remained on treatment at the study visit. In fact, only nine patients reported trastuzumab-related adverse events, the majority of which were mild in severity, and seven patients required treatment modifications. These findings are in line with adverse events previously reported during trastuzumab administration and support its favorable safety profile [23]. This is especially important in routine clinical practice as the potential occurrence of trastuzumab-related toxicities constitutes a key point to consider when tailoring treatment to patients' needs and cardiac toxicity represents a major concern [16]. Nonetheless, in our study, reversible cardiac toxicity was reported in only three patients and treatment modifications due to decreased left ventricular ejection fraction were required in only one. Though most studies on adjuvant therapy with trastuzumab only included younger women [25, 26] and cardiac toxicity risk might increase with age [27], our findings support the safety of trastuzumab administration within a wide range of patient ages. In this regard, a recent retrospective study carried out in patients aged 70 years or older also reported a good safety profile, with rates of any adverse event of 20 % and cardiac events of 14 % [28]. Nevertheless, biases derived from the collection of data already recorded in medical charts cannot be ruled out and further studies are still needed to confirm these findings.

Safety concerns regarding the administration of adjuvant therapies have often led to consider that elderly women with breast tumors might not be equally treated [29]. Given the importance of age and the fact that most studies have not considered the inclusion of elderly populations, we were interested in comparing the therapies used in patients <70 and ≥ 70 years old. In our study, no significant differences were observed in the administration of the different adjuvant therapies, with only a non-significant trend to use chemotherapy less frequently in patients aged ≥ 70 years. Current medical care improvements and increased awareness of the importance of healthy lifestyles might have contributed to a better health status at an older age that might have enabled adjuvant treatments to still be administered to certain elderly patients. In fact, our findings are in agreement with data coming from different trials

and retrospective analyses reporting that older patients in good health may have adequate tolerance of adjuvant treatments, with a toxic profile similar to that observed in younger patients [30, 31]. However, in our study, the patient population aged ≥ 70 years only constituted 12 % of the sample size, reinforcing the need for further assessments in larger patient populations to achieve stronger evidence.

Additional study limitations such as those derived from the collection of data from medical charts should be considered when interpreting the study results. Moreover, data related to disease outcomes such as relapse-free survival or overall survival were not retrieved in this study, which precluded the assessment of treatment efficacy. Though we acknowledge that the study results should be interpreted with caution based on the previously mentioned limitations, we would also like to highlight that the achievement of the planned sample size needed to fulfill the primary objective supports the representativeness of its findings. Furthermore, the observational nature of the study and its multicenter design—with 27 participating hospitals—enhance the generalizability of the study results. Therefore, we believe that this study provides physicians with meaningful information to consider when managing small HER2-positive breast cancer in daily clinical practice.

In conclusion, our study expanded the information currently available on the adjuvant regimens with trastuzumab used for small HER2-positive breast cancer in routine clinical practice, showing that trastuzumab-based adjuvant treatment of small HER2-positive breast cancer is mostly based on chemotherapy—mainly paclitaxel/docetaxel. Further combinations include its administration together with hormone therapies—mainly letrozole and tamoxifen—and radiotherapy was also administered according to clinical practice. These findings suggest that the treatment patterns used for small HER2-positive breast cancer are similar to those used for larger tumors. Furthermore, the addition of trastuzumab to the adjuvant therapy was well tolerated and showed a very low incidence of cardiac events, which represents a key factor to consider when deciding on the most suitable therapy. Nevertheless, further research still needs to be done to confirm our findings and to provide further evidence to optimize the administration of trastuzumab for small HER2-positive tumors.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study was conducted in accordance with the World Medical Association Declaration of Helsinki, all its amendments, and national regulations. The study was approved by the Clinical Research Ethic Committee of Galicia (Santiago de Compostela, Spain) and all patients gave their informed consent before study enrollment.

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