DOI: 10.1590/1413-81232023286.15092022EN

Effectiveness of adjuvant trastuzumab in women with HER-2+ breast cancer in the SUS

Joanna d'Arc Lyra Batista (http://orcid.org/0000-0002-3703-2845) [1,2]
Rafael José Vargas Alves (http://orcid.org/0000-0002-6294-917X) [3]
Taís Belladona Cardoso (http://orcid.org/0000-0003-2968-7275) [3]
Marcelo Moreno (http://orcid.org/0000-0003-0244-9138) [1]
Katsuki Arima Tiscoski (http://orcid.org/0000-0003-0074-4272) [3]
Carisi Anne Polanczyk (http://orcid.org/0000-0002-2447-2577) [2]

Abstract *The aim of this study was to evaluate the effectiveness in a real-world study of adjuvant trastuzumab in women with HER-2+ initial breast cancer in overall survival and recurrence-free survival. A retrospective cohort study was conducted with women who had HER-2+ breast cancer treated with trastuzumab from July 2012 to May 2017 and followed up until July 2021. The death rate was 2.62 per 100 persons/year, and the incidence rate of recurrence was 7.52 per 100 persons/year. The probability of survival at 8.7 years was 85.9%, while the probability of recurrence-free survival in the same period was 62.8%. The use of trastuzumab proved to be effective in the adjuvant treatment of breast cancer in a public health service in southern Brazil. Prognostic factors associated with worse overall survival or relapse did not influence the natural history of the disease, except locally advanced disease at the beginning of treatment. The data presented may prove to be useful in helping to make decisions about whether to use trastuzumab in the treatment of initial or locally advanced breast cancer in the Brazilian SUS.*

Key words *Trastuzumab, Breast neoplasms, Effectiveness*

[1] Universidade Federal da Fronteira Sul. Rodovia SC 459, Km 02, Sala 317, Fronteira Sul. 89801-001 Chapecó SC Brasil. joanna.batista@uffs.edu.br
[2] Instituto de Avaliação de Tecnologia em Saúde. Porto Alegre RS Brasil.
[3] Irmandade da Santa Casa de Misericórdia de Porto Alegre. Porto Alegre RS Brasil.

Introduction

In Brazil, approximately 625,000 new cases of cancer will occur in 2020 through 2022, with the most frequent types being prostate cancer in men and breast cancer in women (excluding nonmelanoma skin tumors). Breast cancer is the most common cancer overall and has the highest mortality rate; in 2020 alone, there were 66,280 new cases, 4,050 of these were in the state of Rio Grande do Sul[1]. The estimated risk of breast cancer is 71.2 cases per 100,000 inhabitants in the Southern region of Brazil[1].

Although breast cancer has a relatively good prognosis if diagnosed and treated early, mortality rates from this type of cancer remain high in Brazil[1]. In 2019, 18,068 women died from breast cancer[2].

Overexpression or amplification of human epidermal growth Factor 2 (HER-2) occurs in 18-30% of malignant breast neoplasms[3]. Neoplasms that overexpress HER-2 receptors have been identified as an aggressive type with a high recurrence rate after adjuvant chemotherapy[3]. The development of monoclonal antibodies directed at the HER-2 receptor, such as trastuzumab, has shown benefits in terms of overall and recurrence-free survival when used in adjuvant or neoadjuvant treatment of breast cancer associated with chemotherapy[4,5].

Trastuzumab was recommended for coverage by the Unified Health System (SUS) per the recommendation of the National Commission for the Incorporation of SUS Technologies (CONITEC) in 2012 for the treatment of early and locally advanced breast cancer[6,7]. However, the profile of patients treated after approval of a new medication may be different from that of patients enrolled in clinical trials. That is why studies with real-life data are important because they evaluate the clinical impact of new health technologies in patients who are often not represented in clinical studies. Thus, evaluating the impact of a new modality and verifying benefits observed in clinical studies are confirmed in more heterogeneous populations is essential, especially in determining whether the new technology should be retained[8].

To date, there has been no evaluation of the clinical impact of trastuzumab in the SUS, according to the recommendations of CONITEC[6,7]. Therefore, the objective of this study was to evaluate the effectiveness of trastuzumab (adjuvant or neoadjuvant) in women with HER-2+ breast cancer who received their treatment exclusively through the public health service.

Methods

The present study was an arm of a larger project entitled "Determination of the prevalence, survival and mortality of cancer patients who received treatment and follow-up at a reference hospital in southern Brazil: A retrospective study with data from the Hospital Cancer Registry".

This was a retrospective cohort study that analyzed survival data from the Hospital Cancer Registry (RHC) of a reference philanthropic hospital in the city of Porto Alegre-RS. Recruitment was based on the results of molecular tests, which classified the HER-2+ status of the tumor, and anatomopathological tests available at the RHC of the Santa Casa de Misericórdia in Porto Alegre of patients diagnosed with breast cancer from July 2012 to May 2017 with follow-up ending on July 31, 2021. Data collection was performed with patients diagnosed as of July 2012 immediately after the inclusion of trastuzumab by CONITEC.

Complementary data not available in the RHC were retrieved by actively searching the medical records of the included patients. The variables collected were reviewed by two oncologists. The inclusion criteria were women diagnosed with HER-2 (including luminal HER-2) breast cancer, confirmed by molecular examination silver in situ hybridization (SISH) or fluorescence in situ hybridization (FISH) and who were within the CONITEC recommended inclusion criteria[6,7]. Women whose medical care was transferred from the study hospital to another source after diagnosis were excluded. The outcome death was verified through the Mortality System at the Center for Health Information of the state of Rio Grande do Sul (Source SIM/NIS/DGTI/SES/RS).

The dependent variable or event of interest was the time between the date of diagnosis to relapse (locoregional or distant) in the case of relapse-free survival or until death in the case of overall survival. The follow-up time for the cases considered censored was the time elapsed from diagnosis to the date of the last consultation, which was assessed at the end of the study period on July 31, 2021. Outcomes were collected from the RHC and medical records. The variables studied were selected according to those in the registry: biological (age range and menopausal status), clinical (staging, neoadjuvant or adjuvant chemotherapy, surgery, endocrine therapy and drop in ejection fraction) and follow-up (recurrence and death). The descriptions of stages came from the 7th edition of the American Joint Committee on Cancer (AJCC).

Recurrence was defined by the evidence of recurrence on imaging (mammography, CT scans and bone scintigraphy) and, when available, confirmed by anatomopathological examination.

The records were reviewed by the researchers using a questionnaire developed specifically for the study. The data were entered into a specific database created in the Research Electronic Data Capture (REDCap). REDCap is a secure web platform developed to aid in the collection and storage of data in scientific investigation studies. The software is available free of charge to the more than 4,000 institutions that are part of the consortium, such as Santa Casa de Misericórdia de Porto Alegre.

The data were analyzed using Stata 12 software (Stata-Corp LP®, College Station, TX®). The nonparametric Kaplan-Meier product-limit estimator was used to calculate the overall probability, mean and median time of disease-free survival, stratified by the variable of the final model. The log-rank test was used to compare whether the curves obtained for different categories of the same variable were statistically equivalent.

To identify the use of trastuzumab as associated with relapse and overall death, the simple model and the multiple Cox proportional hazards model were used, using the hazard ratio (HR) as the measure of association. The semiparametric Cox proportional hazards model was chosen because it is a model capable of estimating survival curves when several explanatory variables are studied simultaneously and has been shown to be a very useful model in the study of risk factors and prognoses. The 95% confidence interval was used to assess statistical significance. The variables of the simple model were also analyzed in the *Cox* proportional hazards regression model. The Cox proportional assumption test was performed, which is based on Schoenfeld residuals after defining a model using "*stcox*".

The significant variables ($p \leq 0.20$) in the analysis using the simple model were introduced one by one in the multiple model, according to their statistical significance and clinical-epidemiological importance, and they remained if they presented a statistical significance with a p value <0.05. Cox-Snell residual analysis was performed to estimate the fit of the model.

The study complied with the norms on research ethics contained in Resolution number 466 of 2012 of the National Health Council. The project in which this study is nested was approved by the Research Ethics Committee of the Santa Casa de Misericórdia de Porto Alegre (Opinion number 1,551,721, of May 19, 2016).

Results

The cohort included 92 women diagnosed with breast cancer who were HER-2+ (hormone receptor positive or negative) admitted for treatment at Santa Casa de Misericórdia de Porto Alegre from July 2012 to May 2017. Of these, two patients were lost due to death before starting treatment with trastuzumab, and the final sample consisted of 90 women. All of them used trastuzumab for one year, according to the protocol of an extended regimen of 52 weeks[8]: chemotherapy of HER-2+ breast cancer, confirmed by molecular examination, with high risk of recurrence, in adjuvant therapy (after surgery, initially combined with chemotherapy and until completing one year of trastuzumab), or neoadjuvant (prior to surgery, combined with chemotherapy and continued in monodrug after surgery until completing one year of treatment). Most patients (65.6%) were ages 35 to 59 years, with seven (7.8%) younger than 35 years and 24 (26.7%) 60 years or older. Half lived in other municipalities (50.0%), 35.6% lived in Porto Alegre, and 14.4% had no record of the municipality of residence. Most patients (62.2%) had negative axillae, and 32.2% had affected axilla at diagnosis. Table 1 presents the biological and clinical characteristics of the patients included in the study.

Overall survival analysis

All patients included in the study were followed up for a mean time of 61.8 months (11.5-104.4). The maximum follow-up period of the study was 104.4 months (8.7 years). During the follow-up period, 12 deaths were recorded. Of this total, 11 deaths (91.7%) occurred due to the progression of breast cancer (data not shown in the tables), a rate of 2.62 per 100 person-years.

Figure 1A shows the Kaplan-Meier graph of the probability of overall survival until the final follow-up time, 104.4 months (8.7 years), which was 85.9%. The last death occurred at 46 months (3.8 years).

Table 2 presents the frequencies of the exposure variables studied, grouped into blocks, according to the incidence of death during the study period. In addition, it is possible to verify the simple model of the associations between

Table 1. Characteristics of patients with HER-2-positive breast cancer and complementary treatment with trastuzumab treated at Hospital da Santa Casa de Misericórdia de Porto Alegre, 2012-2017.

Characteristics	N (% valid)
Age	
<35 years	7 (7.8)
35 to 49 years	22 (24.4)
50 to 59 years	37 (41.1)
60 years of age or older	24 (26.7)
Menopause status	
Premenopause	37 (41.1)
Postmenopause	47 (52.2)
No information	6 (6.7)
Commitment of the axilla at diagnosis	
Negative axilla	56 (62.2)
Compromised armpit	29 (32.2)
No information	5 (5.6)
Initial clinical staging*	
I	25 (27.8)
II	46 (51.1)
III	19 (21.1)
Type of surgery	
Conservative surgery	51 (56.7)
Mastectomy	38 (42.2)
No registration	1 (1.1)
Neoadjuvant chemotherapy	
Yes	43 (47.8)
No	47 (52.2)
Type of chemotherapy	
No anthracycline	9 (10.0)
Anthracycline and taxanes	81 (90.0)
Adjuvant endocrine therapy (n=88)	
Yes	52 (59.1)
No	36 (40.9)
Reduction in Ejection Fraction (EF)** (n=88)	
Reduction in EF greater than 10% of baseline, with less than 50% EF	14 (15.9)
Symptomatic CHF: symptoms of CHF + EF reduction >10% from baseline, with EF<50%	5 (5.7)
No drop in EF	69 (78.4)

* Including stages A, B (I, II and III); or C (stage III). ** Six patients discontinued trastuzumab due to cardiac toxicity.

Source: Authors.

the studied factors and the risk of death with the HR, 95% CI and *p* value. The *p* value for the risk proportionality test is also described in the table, and this assumption was respected by all variables ($p>0.05$).

The following factors were included in the regression model: initial cancer stage III (HR 4.25; 95%CI: 1.37-13.2); absence of adjuvant endocrine therapy (HR 2.12; 95%CI: 0.67-6.70); adjuvant chemotherapy (HR 0.38; 95%CI: 0.11-1.26); neoadjuvant chemotherapy (HR 2.50; 95%CI: 0.75-8.30); and premenopausal status (HR 2.59; 95%CI: 0.76-8.86).

The final multivariate Cox regression model of the association between the exposures studied and death respected the assumption of proportionality of hazards (p=0.751). The variable that remained in the final model was the initial stage of cancer classified as III A, B or C with HR=4.25 with a 95%CI of 1.37-13.2 (p=0.012).

Figure 1B shows the estimate of the probability of overall survival using the Kaplan-Meier method and the *log-rank* test, with a 95%CI, stratified by the final model variable: initial cancer stage (I or II A/B; III A, B or C). The *p* value of the *log-rank* test was 0.0064.

Analysis of disease-free survival

During the follow-up period, 31 relapses were recorded. The incidence of recurrence in the cohort during the follow-up period was 7.52 per 100 person-years.

Figure 2A shows the Kaplan-Meier graph of the probability of disease-free survival until the final follow-up time, 104 months (8.7 years), which was 62.8%. The last recurrence was observed at 5.2 years of follow-up.

The frequencies of the exposure variables (grouped into blocks, according to the incidence of relapse during the total study period) and the simple model of the associations between the factors studied and the risk for relapse with HR, 95%CI and *p* value are presented in Table 3. It is also possible to verify the *p* value for the risk proportionality test. This assumption was respected by all variables ($p>0.05$).

The following were included in the regression model: initial cancer stage III (HR 3.20; 95%CI: 1.55-6.62); neoadjuvant chemotherapy (HR 2.52; 95%CI: 1.20-5.28); adjuvant chemotherapy (HR 0.38; 95%CI: 0.18-0.79); absence of adjuvant endocrine therapy (HR 2.12; 95%CI: 1.04-4.30); and premenopausal status (HR 1.84; 95%CI: 0.88-3.83).

The final multivariate *Cox* regression model of the association between the exposures studied and relapse respected the assumption of hazard proportionality (p=0.564). The variable that remained in the final model was the initial stage of

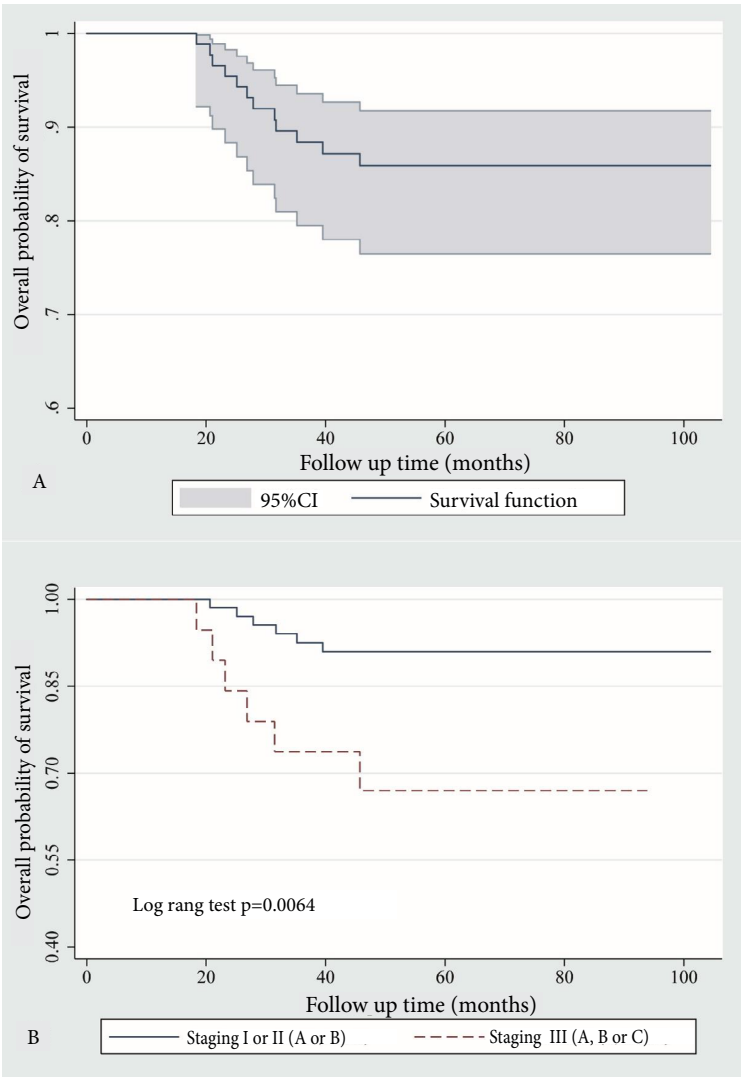

Figure 1. Estimate of the probability of overall survival by Kaplan-Meier analysis. A) At 104.4 months (8.7 years) of follow-up, with 95%CI; B) Stratified by initial staging with log-rank test.

Source: Authors.

cancer classified as III A, B or C with HR=3.05 with 95%CI 1.47-6.33 (p=0.003); not having undergone adjuvant endocrine therapy appeared in the final model with a borderline *p* value of 0.054, HR=2.01 and 95%CI of 0.99-4.10.

Figure 2B shows the estimate of the probability of recurrence-free survival using the Kaplan-Meier method and the *log-rank* test, with a 95%CI, stratified by the variable initial cancer stage (I or II A/B; III A, B or C). The Kaplan-Meier *log-rank* test for equality of curves, when $p<0.05$, confirms the significant differences between the curves.

Quality of fit of the models

The analysis of the Cox-Snell residuals showed that the risk functions are very close to the 45 degree line, and it can be said, based on these results, that the Cox models for overall and recurrence-free survival showed global fit and quality of good predictions (data not shown).

Table 2. Frequency distribution and simple Cox model of biological and clinical factors associated with death in patients with HER-2-positive breast cancer and complementary treatment with trastuzumab treated at Hospital da Santa Casa de Misericórdia de Porto Alegre, 2021.

	Death		HR raw (95%CI)	p	Proportionality test p
	Yes n (%)	No n (%)			
Biological Variables					
Age group					
50 years or older	07 (58.3)	54 (69.2)	1,0		
Less than 50 years old	05 (41.7)	24 (30.8)	1.70 (0.54-5.36)	0.364	0.8880
Menopause status					
Postmenopause	04 (36.4)	43 (58.9)	1.0		
Premenopause	07 (63.6)	30 (41.1)	2.59 (0.76-8.86)	0.129	0.8627
Clinical Variables					
Initial staging of cancer					
I or II (A or B)	06 (50.0)	65 (83.3)	1.0		
III (A, B or C)	06 (50.0)	13 (16.7)	4.25 (1.37-13.2)	0.012	0.7514
Type of surgery performed					
Mastectomy	06 (50.0)	32 (41.0)	1.0		
Conservative surgery	06 (50.0)	46 (59.0)	0.70 (0.23-2.18)	0.543	0.2911
Neoadjuvant chemotherapy					
No	04 (33.3)	44 (56.4)	1.0		
Yes	08 (66.7)	34 (43.6)	2.50 (0.75-8.30)	0.135	0.9702
Adjuvant chemotherapy					
No	08 (66.7)	33 (42.3)	1.0		
Yes	04 (33.3)	45 (57.7)	0.38 (0.11-1.26)	0.114	0.9643
Type of chemotherapy					
No anthracycline	01 (8.33)	08 (10.3)	1.0		
Anthracycline and taxanes	11 (91.7)	70 (89.7)	1.17 (0.15-9.07)	0.880	0.7549
Adjuvant endocrine therapy					
Yes	05 (41.7)	47 (61.8)	1.0		
No	07 (58.3)	29 (38.2)	2.12 (0.67-6.70)	0.198	0.7619
Decreased ejection fraction					
No	08 (66.7)	61 (80.3)	1.0		
Yes	04 (33.3)	15 (19.7)	1.80 (0.54-5.98)	0.337	0.0762

HR: hazard ratio; 95%CI: 95% confidence interval.

Source: Authors.

Discussion

The data analyzed belonged to the first patients who underwent treatment with trastuzumab in the Brazilian Public Health System (SUS) in a referral hospital in southern Brazil. The mean follow-up time was 61.8 months (11.5-104.4). The overall survival and recurrence-free survival rates at 8.7 years were 85.9% and 62.8%, respectively. In the multivariate analysis, it was observed that the variable stage III was considered an independent risk factor for both disease recurrence and mortality and that not having undergone adjuvant endocrine therapy resulted in a borderline *p* value and may be a risk factor for recurrence of the disease.

The HERA[4] study was the first randomized phase III clinical trial to show a significant improvement in overall survival in women with HER2+ breast cancer with the addition of trastuzumab to adjuvant chemotherapy compared to chemotherapy alone. After the publication of HERA, a series of clinical studies[9-12] with the same objectives were published, corroborating the findings of the HERA trial. The subjects in these studies were mostly patients with breast cancer and positive axillary lymph nodes or negative axillary lymph nodes with high-risk tumors.

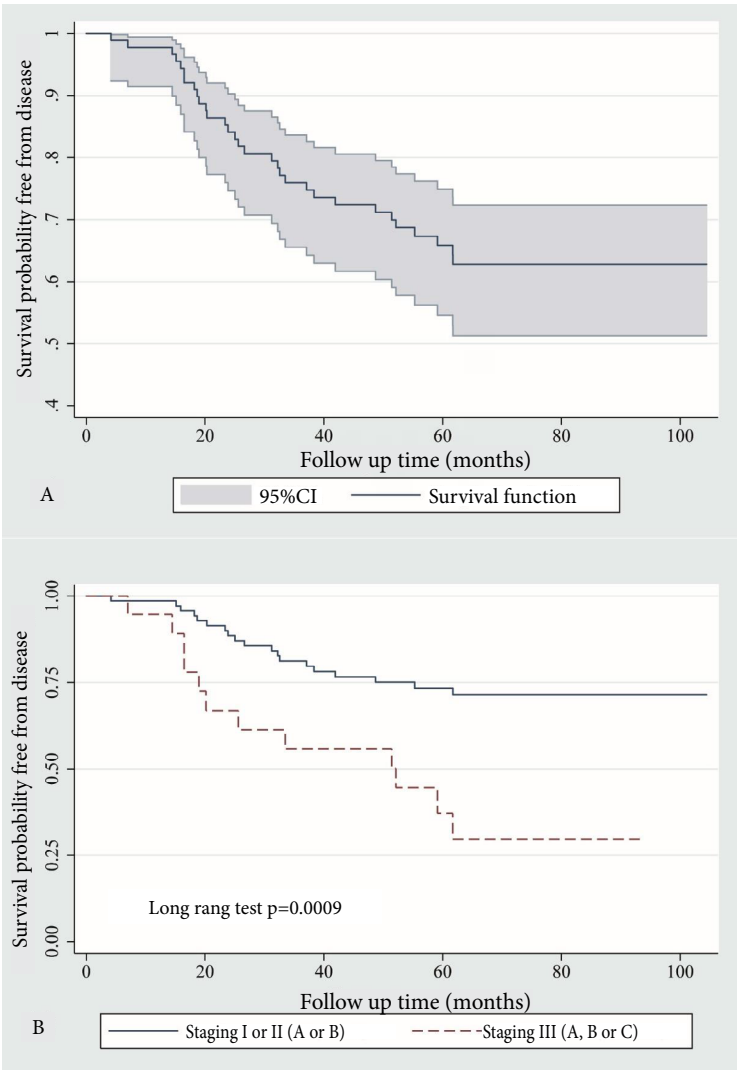

Figure 2. Estimation of the probability of recurrence-free survival by Kaplan-Meier analysis. A) At 104.4 months (8.7 years) of follow-up, with 95%CI; B) Stratified by initial staging with log-rank test.

Source: Authors.

This patient profile is similar to that of our study, in which 32.2% of our subjects had compromised axilla at diagnosis and 62.2% had negative axilla but with high-risk tumors. Other sample characteristics that are similar to the clinical studies are as follows: the majority were menopausal women (52.2%), undergoing breast-conserving surgery (56.7%) and using adjuvant hormone therapy (59.1%).

In the HERA[4,5,13,14] and FNCLCC-PACS 04[10] studies, patients were allocated to trastuzumab or observation groups after completion of chemotherapy, that is, sequential administration. The patients included in the NSABP B-3[9] study and a group of patients in the NCCTG-N9831[9] and BCIRG 006[11,12] studies received trastuzumab concomitantly with taxane. This variability in trastuzumab administration had no impact on the clinical outcomes of the studies. Differences in trastuzumab administration were also observed in our study, in which 52.2% of the patients received adjuvant trastuzumab with sequential

Table 3. Frequency distribution and simple Cox model of the biological and clinical factors associated with recurrence in patients with HER-2-positive breast cancer and complementary treatment with trastuzumab treated at Hospital da Santa Casa de Misericórdia de Porto Alegre, 2021.

	Recurrence		HR raw (95%CI)	*p*	Proportionality test
	Yes n (%)	No n (%)			p
Biological Variables					
Age group					
50 years or older	20 (64.5)	41 (69.5)	1.0		
Less than 50 years old	11 (35.5)	18 (30.5)	1.32 (0.63-2.76)	0.455	0.4150
Menopause status					
Postmenopause	13 (44.8)	34 (61.8)	1.0		
Premenopause	16 (55.2)	21 (38.2)	1.84 (0.88-3.83)	0.102	0.3731
Clinical Variables					
Initial staging of cancer					
I or II (A or B)	19 (61.3)	52 (88.1)	1.0		
III (A. B or C)	12 (38.7)	07 (11.9)	3.20 (1.55-6.62)	0.002	0.5083
Type of surgery performed					
Mastectomy	15 (48.4)	23 (39.0)	1.0		
Conservative surgery	16 (51.6)	36 (61.0)	0.73 (0.36-1.47)	0.382	0.9010
Neoadjuvant chemotherapy					
No	11 (35.5)	37 (62.7)	1.0		
Yes	20 (64.5)	22 (37.3)	2.52 (1.20-5.28)	0.014	0.8786
Adjuvant chemotherapy					
No	20 (64.5)	21 (35.6)	1.0		
Yes	11 (35.5)	38 (64.4)	0.38 (0.18-0.79)	0.010	0.8613
Type of chemotherapy					
No anthracycline	01 (3.2)	08 (13.6)	1.0		
Anthracycline and taxanes	30 (96.8)	51 (86.4)	3.28 (0.45-24.0)	0.243	0.1367
Adjuvant endocrine therapy					
Yes	14 (45.2)	38 (66.7)	1.0		
No	17 (54.8)	19 (33.3)	2.12 (1.04-4.30)	0.038	0.4081
Decreased ejection fraction					
No	25 (80.6)	44 (77.2)	1.0		
Yes	06 (19.4)	13 (22.8)	0.86 (0.35-2.10)	0.742	0.8217

HR: hazard ratio; 95%CI: 95% confidence interval.

Source: Authors.

variants or concomitantly with taxane, while the remaining patients received neoadjuvant therapy (concomitant with taxane). All patients without cardiac toxicity or recurrence in less than one year used trastuzumab for 12 months, which is in agreement with the literature.

The effectiveness of trastuzumab has been evaluated in different clinical studies[5,9-17] where the reported disease-free survival ranges from 72% to 92%. Despite all the limitations, such as methodological differences, differences in follow-up time and sample size, some inferences are relevant: in the present study, the estimated probability of disease-free survival up to 8.7 years was 62.8%, lower than the survival rate reported in studies with shorter follow-up[9-11,17]. As expected, a greater number of relapses was documented in the study that followed the patients for a longer period of time (11 years)[5]. In other studies that included patients with clinical characteristics similar to those in the present study, the recurrence-free survival rate ranged from 66% to 94%[4,11-18]. This variation also depended on the stage of disease at diagnosis; patients with more advanced stages at diagnosis had a higher recurrence rate, and the length of the follow-up period (three to 10 years), where those who were evaluated over a shorter period of time had fewer relapse events compared to those

evaluated over a longer period of time[18-22]. In the present study, the variable stage III at the time of diagnosis was found to be an isolated risk factor for a greater risk of relapse, which corroborates previous studies.

Adjuvant therapy with trastuzumab was well established for early HER2+ breast cancer in a recent systematic review[23] with considerable survival benefits. As most data on the benefit of trastuzumab come from clinical studies conducted in selected populations, it is important to evaluate the results in scenarios with real-world data, especially in Brazil, since systematic reviews are based on international studies. A study conducted in Turkey, which evaluated 210 patients in the early stages of breast cancer treated with trastuzumab, found a three-year overall survival of 92%. The only factor statistically associated with worse prognosis in the multivariate analysis was histological grade III primary neoplasia[18].

In a Serbian study that evaluated the outcomes of disease-free interval and overall survival at 10 years after the use of trastuzumab (with a mean follow-up of 69 months), the overall survival was 81.8%, which was significantly higher in patients with small tumors, a smaller number of affected lymph nodes and a lower stage of disease[19]. Another retrospective analysis performed in ten Italian cancer centers compared two cohorts of patients who had received adjuvant chemotherapy with or without the addition of trastuzumab[20]. The overall survival rates at five years were 88.4% and 96%, respectively (p<0.01). A study conducted in 56 Japanese institutions that included women with HER2+ stage I-IIIC breast cancer described an overall survival rate of 98.9% at three years[21].

Previous studies have shown that patients who express hormone receptors and do not undergo adjuvant endocrine therapy have a worse prognosis and a higher risk of recurrence. The meta-analysis of the EBCTCG[24] showed that patients who received adjuvant endocrine therapy with tamoxifen for five years had a 30% reduction in breast cancer mortality, regardless of age, nodal status or use of chemotherapy, which may explain the greater protection against disease recurrence in the group receiving this therapy.

Regarding safety, it was observed that 21.6% of the patients presented cardiac toxicity (decrease in ejection fraction greater than 10% compared to baseline); however, only 5.7% presented symptoms of heart failure. The incidence of cardiac toxicity is considered high (21.6%) because meta-analysis data show that the incidence in the literature is 12% (95%CI 11.3%-12.9%)[25]. This difference may be due to two factors: first, the mean age of the sample (67.8% over 50 years of age) is considered a risk factor for cardiac toxicity; thus, the advanced age of the patients in the study allows us to infer that there may be a considerable prevalence of cardiovascular risk factors, which are also associated with cardiac toxicity caused by trastuzumab; the second factor is the previous use of anthracyclines by the patients in the sample (90%), which is also associated with the development of cardiac toxicity[25]. In meta-analyses, trastuzumab was shown to be effective in terms of increased overall and disease-free survival, but its use should be evaluated individually because it has a two- to three-fold greater risk of cardiotoxicity[26]. Even though a high rate of cardiac toxicity was observed in the study sample, no fatal toxicities related to treatment with trastuzumab were observed, which should be considered in the risk-benefit assessment of therapeutic choice.

Evaluations performed with real-life data also have methodological limitations, as in most retrospective studies: insufficient data collection, lack of information on a particular variable or selection bias[27]. Thus, the present study used some strategies to minimize the effects of these limitations: first, we used data collected in a systematic way, following a predefined methodology by the Cancer Registry System of the National Cancer Institute, in which data quality assessment was performed internally and externally (review of medical records by two oncologists) ensuring data integrity; second, mortality data were checked using the database of the Center for Health Information of the state of Rio Grande do Sul. This nucleus concentrates all the information on death certificates issued in the state of Rio Grande do Sul, which reinforces the quality of this variable in the present analysis. Third, the evaluated population consisted only of patients who were only treated in the SUS, therefore, a representative population in which the CONITEC analysis was performed.

Another limitation of the study is the absence of a control group, but the objective of the study was to evaluate the incorporation of trastuzumab into the Brazilian public health system. Given that the medication was approved for use in July 2012, it would be unethical not to offer trastuzumab to patients with breast cancer and HER2+.

Conclusion

The present study showed with real-world data that patients with HER2-+ early or locally advanced breast cancer who received adjuvant or neoadjuvant trastuzumab in the SUS had overall and recurrence-free survival rates similar to those observed in SUS international clinical trials.

The data presented here may prove useful in deciding whether to maintain the use of trastuzumab in the treatment of early or locally advanced breast cancer in the Brazilian public health service, especially for the southern region of Brazil.

Collaborations

JDL Batista and CA Polanczyk contributed to the design and planning of the study. RJV Alves, TB Cardoso and KA Tiscoski contributed to the construction of the research instruments and performed the data collection. JDL Batista performed the data analysis. JDL Batista, RJV Alves, TB Cardoso and M Moreno contributed to the interpretation of the data. JDL Batista, RJV Alves, TB Cardoso, KA Tiscoski and M Moreno prepared and revised the manuscript. All authors approved the final version of the article. The authors declare no conflicts of interest.

Funding

The study was sponsored and coordinated by Hospital Moinhos de Vento in partnership with the Ministério da Saúde through the Programa de Desenvolvimento Institucional do Sistema Único de Saúde (PROADI-SUS) (Project 01553 - ATS/PROADI HMV).

Data repository Scielo Data: https://doi.org/10.48331/scielodata.KG1BRG

References

1. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Coordenação de Prevenção e Vigilância. *Estimativa 2020: incidência de câncer no Brasil* [Internet]. Rio de Janeiro; 2020 [acessado 2022 jan 20]. Disponível em: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/estimativa-2020-incidencia-de-cancer-no-brasil.pdf.
2. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Coordenação de Prevenção e Vigilância. *Atlas da mortalidade* [Internet]. Rio de Janeiro; 2021 [acessado 2022 jan 20]. Disponível em: https://www.inca.gov.br/app/mortalidade.
3. Parakh S, Gan HK, Parslow AC, Burvenich IJG, Burgess AW, Scott AM. Evolution of anti-HER2 therapies for cancer treatment. *Cancer Treat Rev* 2017; 59:1-21.
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353(16):1659-1672.
5. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, Azambuja E, Castro Jr G, Untch M, Smith I, Gianni L, Baselga J, Al-Sakaff N, Lauer S, McFadden E, Leyland-Jones B, Bell R, Dowsett M, Jackisch C; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017; 389(10075):1195-1205.
6. Brasil. Ministério da Saúde (MS). *Trastuzumabe para tratamento do câncer de mama inicial. Relatório de Recomendação da Comissão Nacional de Incorporação de Tecnologias no SUS – CONITEC – 07* [Internet]. Brasília: MS; 2012 [acessado 2022 mar 13]. Disponível em: http://conitec.gov.br/images/Relatorios/2012/Trastuzumabe_cainicial_final.pdf.
7. Brasil. Ministério da Saúde (MS). *Trastuzumabe para tratamento do câncer de mama avançado. Relatório de Recomendação da Comissão Nacional de Incorporação de Tecnologias no SUS – CONITEC – 08* [Internet]. Brasília: MS; 2012 [acessado 2022 mar 13]. Disponível em: http://conitec.gov.br/images/Relatorios/2012/Trastuzumabe_caavancado_final.pdf.
8. Brasil. Ministério da Saúde (MS). *Diretrizes Diagnósticas e Terapêuticas do Carcinoma de Mama* [Internet]. Brasília, DF; 2018 [acessado 2022 set 20]. Disponível em: https://www.gov.br/conitec/pt-br/midias/consultas/relatorios/2018/relatorio_ddt_carcionomademama_julho_2018.pdf.
9. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353(16):1673-1684.
10. Spielmann M, Roché H, Delozier T, Canon JL, Romieu G, Bourgeois H, Extra JM, Serin D, Kerbrat P, Machiels JP, Lortholary A, Orfeuvre H, Campone M, Hardy-Bessard AC, Coudert B, Maerevoet M, Piot G, Kramar A, Martin AL, Penault-Llorca F. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. *J Clin Oncol* 2009; 27(36):6129-6134.
11. Slamon DJ, Eiermann W, Robert NJ, Giermek J. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC*T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC*TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. *Cancer Res* 2016; 76(Supl. 4):S5-04.
12. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365(14):1273-1283.
13. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, Untch M, Smith I, Baselga J, Jackisch C, Cameron D, Mano M, Pedrini JL, Veronesi A, Mendiola C, Pluzanska A, Semiglazov V, Vrdoljak E, Eckart MJ, Shen Z, Skiadopoulos G, Procter M, Pritchard KI, Piccart-Gebhart MJ, Bell R; Herceptin Adjuvant (HERA) Trial Study Team. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 2011; 12(3):236-244.
14. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013; 382(9897):1021-1028.
15. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, Lortholary A, Espié M, Fumoleau P, Serin D, Jacquin JP, Jouannaud C, Rios M, Abadie-Lacourtoisie S, Tubiana-Mathieu N, Cany L, Catala S, Khayat D, Pauporté I, Kramar A; PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013; 14(8):741-748.
16. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, Utriainen T, Kokko R, Hemminki A, Tarkkanen M, Turpeenniemi-Hujanen T, Jyrkkiö S, Flander M, Helle L, Ingalsuo S, Johansson K, Jääskeläinen AS, Pajunen M, Rauhala M, Kaleva-Kerola J, Salminen T, Leinonen M, Elomaa I, Isola J; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006; 354(8):809-820.

17. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, Utriainen T, Turpeenniemi-Hujanen T, Jyrkkiö S, Möykkynen K, Helle L, Ingalsuo S, Pajunen M, Huusko M, Salminen T, Auvinen P, Leinonen H, Leinonen M, Isola J, Kellokumpu-Lehtinen PL. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009; 27(34):5685-5692.
18. Ulas A, Kos T, Avci N, Cubukcu E, Olmez OF, Bulut N, Degirmenci M. Patients with HER2-positive early breast cancer receiving adjuvant trastuzumab: clinicopathological features, efficacy, and factors affecting survival. *Asian Pac J Cancer Prev* 2015; 16(4):1643-1649.
19. Cvetanovic A, Filipovic S, Zivkovic N, Popovic L, Kostic M, Djordjevic M, Karanikolic A, Krtinic D. Ten years of using adjuvant trastuzumab in breast cancer in Serbia - Single institution experience. *J BUON* 2018; 23(2):353-360.
20. Vici P, Pizzuti L, Natoli C, Moscetti L, Mentuccia L, Vaccaro A, Sergi D, Di Lauro L, Trenta P, Seminara P, Santini D, Iezzi L, Tinari N, Bertolini I, Sini V, Mottolese M, Giannarelli D, Giotta F, Maugeri-Saccà M, Barba M, Marchetti P, Michelotti A, Sperduti I, Gamucci T. Outcomes of HER2-positive early breast cancer patients in the pre-trastuzumab and trastuzumab eras: a real-world multicenter observational analysis. The RETROHER study. *Breast Cancer Res Treat* 2014; 147(3):599-607.
21. Yamshiro H, Iwata H, Masuda N, Yamamoto N, Nishimura R, Ohtani S, Sato N, Takahashi M, Kamio T, Yamazaki K, Saito T, Kato M, Lee T, Ohno S, Kuroi K, Takano T, Takada M, Yasuno S, Morita S, Toi M. Outcomes of trastuzumab therapy in HER2-positive early breast cancer patients. *Int J Clin Oncol* 2015; 20(4):709-722.
22. Mustacchi G, Puglisi F, Molino AM, Crivellari D, Ghiotto C, Ferro A, Brunello A, Saracchini S, Turazza M, Cretella E, Iop A, Malagoli M, Stefani M. Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients. *Future Oncol* 2015; 11(10):1493-1500.
23. Wilson FR, Coombes ME, Brezden-Masley C, Yurchenko M, Wylie Q, Douma R, Varu A, Hutton B, Skidmore B, Cameron C. Herceptin® (trastuzumab) in HER2-positive early breast cancer: a systematic review and cumulative network meta-analysis. *Syst Rev* 2018; 7:191.
24. Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patientlevel meta-analysis of randomised trials. *Lancet* 2011; 378:771-784.
25. Jawa Z, Perez RM, Garlie L, Singh M, Qamar R, Khandheria BK, Jahangir A, Shi Y. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: A meta-analysis. *Medicine (Baltimore)* 2016; 95(44):e5195.
26. Genuino AJ, Chaikledkaew U, The DO, Reungwetwattana T, Thakkinstian A. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2019; 12(8):815-824.
27. Khozin S, Blumenthal GM, Pazdur R. Real-world Data for Clinical Evidence Generation in Oncology. *J Natl Cancer Inst* 2017; 109:11.

Article submitted 11/07/2022
Approved 04/11/2022
Final version submitted 06/11/2022

Chief editors: Romeu Gomes, Antônio Augusto Moura da Silva