BJO
Brazilian Journal of Oncology

ORIGINAL ARTICLES CLINICAL ONCOLOGY

Analysis of trastuzumab therapy's efficacy with or without pertuzumab combination in the metastatic HER2-positive breast cancer an oncology hospital of Pernambuco

Análise da eficácia da terapia com trastuzumabe com ou sem combinação de pertuzumabe no câncer de mama HER2-positivo metastático em um hospital oncológico de Pernambuco

Kaline Nascimento dos Santos Lima[1], Juvanier Romão Cruz[1], Amanda Florentino Fonseca de Carvalho

ABSTRACT

Objectives: To evaluate the efficacy between trastuzumab-only or pertuzumab plus trastuzumab therapies in metastatic HER2-positive breast cancer patients. **Material and Methods:** At Hospital de Cancer de Pernambuco (HCP), Recife, Brazil, a cross-sectional study was carried out. One hundred seventy-two patients with HER2-positive metastatic breast cancer (BC) were divided into two groups. One group of patients underwent chemotherapy with trastuzumab-only between 2013 and 2016, and another group underwent treatment with pertuzumab plus trastuzumab (P+H) between 2017 and 2020. **Results:** The median age was 50.4 years (range 25-86) when diagnosed with tumor metastasis. The patients treated with trastuzumab-only had a mortality rate of 13/100 women per year (95% CI: 9.19 to 18.38), and those treated with trastuzumab plus pertuzumab had a mortality rate of 4.14/100 women per year (95% CI: 2.50 to 6.87). The estimated risk ratio (HR) for the trastuzumab-only group was 3.16-fold higher death than the P+H-treated group. The group of patients who evolved into metastasis during follow-up had a risk 3.12-fold higher of death compared to the group in tumor metastases at early diagnosis. In the multivariate analysis, the HR estimate adjusted for the trastuzumab-only treated group was 3.58-fold higher death than the P+H group. The mean follow-up time was three years (15 days to 14.7 years). The estimated mortality rate was 7.73/100 diagnosed women per year (95% CI: 5.80 to 10.3). In the analysis of overall survival (OS), there was a significant difference between the groups treated with trastuzumab-only or P+H (p<0.0001). **Conclusion:** There are benefits in incorporating new therapies into Brazil's public health network for the treatment of women with metastatic HER2-positive breast cancer, impacting increased OS and better quality of life, even those diagnosed in more advanced stages.

Keywords: Breast neoplasms; Receptor, ErbB-2; Antibodies, Monoclonal.

1. Hospital de Câncer de Pernambuco, Oncologia - Recife - Pernambuco - Brazil.

Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.
Correspondence author: Kaline Nascimento dos Santos Lima.
E-mail: kalinensantos@hotmail.com

Received on: Feb 25, 2022 | **Accepted on:** Apr 8, 2022 | **Published on:** Jun 22, 2022
DOI: https://doi.org/10.5935/2526-8732.20220339

RESUMO

Objetivos: Avaliar a eficácia entre terapias apenas com trastuzumabe ou pertuzumabe mais trastuzumabe, em pacientes com câncer de mama HER2-positivo metastático. **Material e Métodos:** Foi realizado um estudo transversal no Hospital de Câncer de Pernambuco (HCP), Recife, Brasil. Cento e setenta e dois pacientes com câncer de mama (CM) HER2-positivo metastático foram divididos em dois grupos. Um grupo de pacientes foi submetido à quimioterapia apenas com trastuzumabe, entre 2013 e 2016; e outro grupo foi submetido ao tratamento com pertuzumabe mais trastuzumabe (P+H) entre 2017 e 2020. **Resultados:** A idade mediana foi de 50,4 anos (variação 25-86) quando diagnosticada com metástase tumoral. Os pacientes tratados apenas com trastuzumabe tiveram uma taxa de mortalidade de 13/100 mulheres por ano (IC 95%: 9,19 a 18,38), e aqueles tratados com trastuzumabe mais pertuzumabe tiveram uma taxa de mortalidade de 4,14/100 mulheres por ano (IC 95%: 2,50 a 6,87). A razão de risco estimada (HR) para o grupo tratado apenas com trastuzumabe foi 3,16 vezes maior que o grupo tratado com P+H. O grupo de pacientes que evoluiu para metástase durante o seguimento apresentou risco 3,12 vezes maior de óbito em relação ao grupo em metástases tumorais no diagnóstico precoce. Na análise multivariada, a estimativa de FC ajustada para o grupo tratado apenas com trastuzumabe foi 3,58 vezes maior de óbito do que o grupo P+H. O tempo médio de seguimento foi de três anos (15 dias a 14,7 anos). A taxa de mortalidade estimada foi de 7,73/100 mulheres diagnosticadas por ano (IC 95%: 5,80 a 10,3). Na análise da sobrevida global (SG), houve diferença significativa entre os grupos tratados apenas com trastuzumabe ou P+H (p<0,0001). **Conclusão:** Há benefícios na incorporação de novas terapias na rede pública de saúde do Brasil para o tratamento de mulheres com câncer de mama HER2-positivo metastático, impactando no aumento da SG e melhor qualidade de vida, mesmo naquelas diagnosticadas em estágios mais avançados.

Descritores: Neoplasias mamárias; Receptor, ErbB-2; Anticorpos, Monoclonais.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and is the central public health problem in the world.[1] Breast cancer is a heterogeneous disease with different molecular subtypes in four main patterns: luminal A, luminal B, HER2-positive, and triple-negative.[2] Several factors are related to the increased predisposition for breast cancer, such as hormone use, parity, breastfeeding and hormone replacement therapy,[3] family history of breast/ovarian cancer, obesity, alcohol consumption, and sedentary lifestyle.[4]

Tumors expressing the HER2 receptor are associated with a poor prognosis but benefit from targeted therapies such as trastuzumab and pertuzumab.[5] In Brazil, in 2012, the National Commission for the Incorporation of Technologies (CONITEC) incorporated trastuzumab in the National Relationship of Essential Medicines of Brazil's Unified Public Health System (SUS) for the treatment of HER2-positive BC at the early and locally advanced stages.[6] Later in 2017, CONITEC decided to incorporate trastuzumab and pertuzumab as first-line of HER2-targeted therapies for metastatic HER2-positive BC and was another significant advance for Brazil's public health.[7]

In 2021, the CLEOPATRA study showed that combined trastuzumab plus pertuzumab therapy in metastatic breast cancer was associated with an increase of 15.6 months in overall survival.[8]

Before incorporating the HER2-targeted therapies (trastuzumab plus pertuzumab) into the public service in Brazil, the rate of judicial requests for the free supply of these therapies in the public network was high, generating high costs and significant budgetary impact for Brazilian public health.[9] In this study, we observed an improvement in the overall survival (OS) of the metastatic HER2-positive BC patients who submitted the combined chemotherapy with pertuzumab plus trastuzumab, proving the outstanding achievement of the incorporation of pertuzumab therapy into Brazil's Unified Public Health System (SUS).

In this sense, we saw an improvement in the OS in metastatic HER2-positive BC patients treated with pertuzumab plus trastuzumab, proving the outstanding achievement of incorporating pertuzumab into SUS. Therefore, it is critical to evaluate the efficacy between trastuzumab-only or pertuzumab plus trastuzumab therapies in metastatic HER2-positive breast cancer patients.

MATERIAL AND METHODS

Study design and participants

At Hospital de Cancer de Pernambuco (HCP), Recife, Brazil, a cross-sectional study was carried out. This human study was approved by HCP-approval: CAAE40729520.2.0000.5205. All adult participants provided written informed consent to participate in this study.

One hundred seventy-two patients with HER2-positive metastatic breast cancer were divided into two groups. One group of patients underwent chemotherapy with trastuzumab-only between 2013 and 2016, and another group of patients underwent treatment with pertuzumab plus trastuzumab between 2017 and 2020. The inclusion criteria for the patients were women with invasive breast cancer, HER2 3+ expression, and clinical stage IV (metastatic), according to the 8th edition classification of solid tumors.[10]

Chemotherapy and HER2-targeted therapies

Chemotherapy regimens included a dense dose of adriablastin RD 60mg/m^2 and cyclophosphamide 600mg/m^2 every two weeks, during four cycles followed by paclitaxel 80mg/m^2 everyone week for 12 weeks. Chemotherapy was administered for a median of four cycles (range 2-6 cycles). The combination chemotherapy with trastuzumab-only or pertuzumab plus trastuzumab was performed until one treatment year.

Statistical analysis

The results presented as absolute and relative frequencies for categorical parameters. Continuous normally distributed data are expressed as mean and standard deviation (SD), while continuous non-normally distributed data were in median and Interquartile (IQR). Shapiro-Wilk test was used to evaluate the normality of data distribution. Qualitative variables were analyzed with chi-square and Fisher's exact tests. Unpaired Student's t-test performed continuous data. Kaplan-Meier survival curves with log-rank tests were used to estimate OS. The stratified Cox proportional-hazards model was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI). Multivariate analysis was used Cox regression to estimate the adjusted HR. Data analysis was performed by Stata v. 14.0 software. For all analyzes, values of $p<0.05$ were considered significant.

RESULTS

The median age was 50.4 years (range 25-86) when they were diagnosed with tumor metastasis. The average body surface was 1.67m^2 (Table 1). The patients treated with trastuzumab-only had a mortality rate of 13/100 women per year (95% CI: 9.19 to 18.38). The patients treated with trastuzumab plus pertuzumab had a mortality rate of 4.14/100 women per year (95% CI: 2.50 to 6.87). The estimated risk ratio (HR) for the trastuzumab-only group was 3.16-fold higher of death compared to the trastuzumab plus pertuzumab-treated group (Table 2).

At diagnosis, the patients presented with metastatic clinical stage had a borderline association (p=0.061) with HR 2.34. The group of patients who evolved into metastasis during follow-up had a risk 3.12-fold higher of death compared to the group in tumor metastases at initial diagnosis (Table 3).

In the multivariate analysis, the HR estimate adjusted by age, early clinical stage, time course between diagnosis and evolution to the metastatic stage, it was found that the trastuzumab-only treated group had a risk 3.58-fold higher of death compared to the trastuzumab plus pertuzumab group (Table 4).

The mean follow-up time was three years (range 15 days to 14.7 years) (Figure 1). The estimated mortality rate was 7.73/100 diagnosed women per year (95% CI: 5.80 to 10.3). In the analysis of OS, there was a significant difference between the groups treated with trastuzumab-only or trastuzumab plus pertuzumab (p<0.001) (Figure 2).

Table 1. Clinical variables.

VARIABLES	TOTAL	TRASTUZUMAB	H+P	*p-value*
	N=172	N=69	N=103	
	Mean (±SD)	Mean (±SD)	Mean (±SD)	
Age (years)	50.4 ± 12.1	53.4 ± 12.4	48.3 ± 11.6	0.007[a]
Time course (months)				
Between diagnosis and evolution to metastasis	2.5 (0; 22.9)	3.7 (0; 23.7)	2.3 (0; 21.4)	0.599
Body surface (m^2)	1.67 ± 0.18	1.67 ± 0.16	1.67 ± 0.19	0.908
Age group (years)	N (%)	N (%)	N (%)	
<40	33 (19.2)	8 (11.6)	25 (24.3%)	
>40 ≤59	108 (62.8)	31 (59.4)	67 (65.1%)	0.003[a]
≥60	31 (18.0)	20 (29.0)	11 (10.7%)	

H + P: Trastuzumab plus pertuzumab; SD = Standard deviation.

Table 2. Types of chemotherapy and time course.

VARIABLES	VALUES
Between diagnosis and 1st dose of trastuzumab	**Median (P_{25}; P_{75})**
Time course (months)	6.0 (1.8; 24.7)
Between first and final doses of trastuzumab	**Median (P_{25}; P_{75})**
Time course (days)	535 (463; 594)
Maintenance dose: trastuzumab	**Median (P_{25}; P_{75})**
Time course (days)	402 (347; 448)
Start of treatment: trastuzumab plus pertuzumab	**Median (P_{25}; P_{75})**
Time course (months)	5.0 (0; 11.3)
Drugs acquisition	**N (%)**
Brazilian Ministry of Health	55 (53.9%)
Judicialization	47 (46.1%)

Table 3. Association of treatment outcome with the type of treatment and clinical variables of patients.

VARIABLES	DEATH RATE (/100 peoples-years)	HAZARD RATIO (CI 95%)	*p-value*
HER2-targeted therapies			
Trastuzumab plus pertuzumab	4.14	Reference	-
Trastuzumab	13.0	3.16 (1.71 – 5.86)	**<0.001**[a]
Age group (years)			
<40	6.77	Reference	-
>40 ≤59	8.37	1.26 (0.58 – 2.75)	0.554
≥60	6.25	1.13 (0.39 – 3.30)	0.826
Stage at diagnosis			
I - II	6.88	Reference	-
III - IIIA	7.47	1.31 (0.51 – 3.33)	0.574
IIIB - IIIC	7.87	1.39 (0.61 – 3.16)	0.428
IV	8.51	2.34 (0.96 – 5.73)	**0.061**
Time course between diagnosis and evolution to metastasis			
Same day	9.71	3.12 (1.43 – 7.14)	**0.005**[a]
Up to one years	8.98	1.49 (0.68 – 3.33)	0.316
Over one years	6.37	Reference	

[a] Statistically significant: $p<0.05$.

Table 4. Multivariate analysis.

VARIABLES	HAZARD RATIO (CI 95%)	*p-value*
HER2-targeted therapies		
Trastuzumab plus pertuzumab	Reference	-
Trastuzumab	3.58 (1.89 – 6.78)	<0.001[a]

[a]Adjusted for age, early clinical staging and time course: between diagnosis and evolution to metastasis.

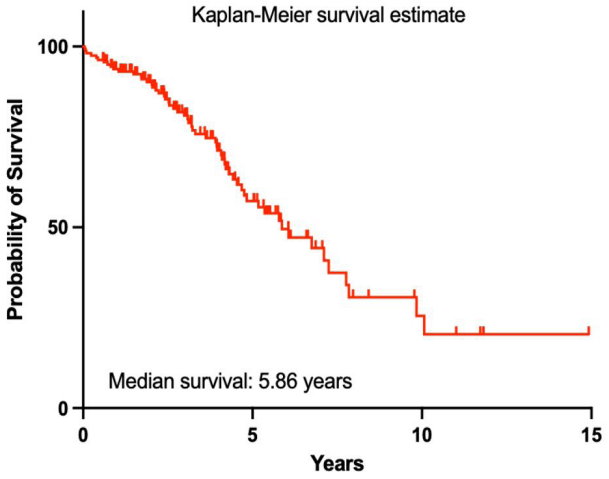
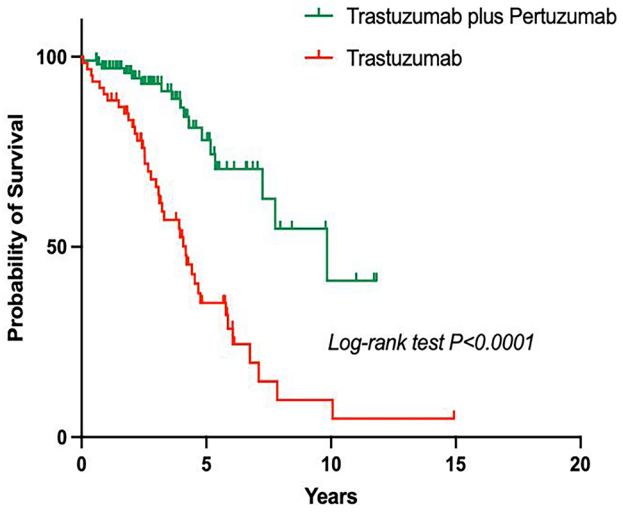


Figure 1. Kaplan-Meier survival curve of metastatic HER2-positive breast cancer patients.



Median survival	
Trastuzumab	4.178
Trastuzumab plus Pertuzumab	9.839
Ratio (and its reciprocal)	0.4246
95% CI of ratio	0.2402 to 0.7506

Figure 2. Overall survival curves in metastatic HER2-positive breast cancer patients treated with trastuzumab or trastuzumab plus pertuzumab.

DISCUSSION

In the present study, patients with breast cancer and metastatic stage at diagnosis had a median age of 50.4 years (range 25 to 86 years), comparable results reported in a previous observational study.[11] There is not only one risk factor for breast cancer, but age over 50 is also considered the most important because when the incidence rate is considered, the number of women with breast cancer and age over 50 rapidly increases. Therefore, the World Health Organization (WHO) and the Brazilian Ministry of Health recommend screening by mammography examination every two years in age over 50.[12]

The mortality rate was higher in the patients treated with trastuzumab-only than those treated with trastuzumab plus pertuzumab. Our results confirm the CLEOPATRA phase III study, despite the limitation that we did not evaluate the association with paclitaxel use.[13] In turn, OS was longer in the trastuzumab plus pertuzumab group than trastuzumab-only. A retrospective study in Singapore (2020)[13] showed more benefits for patients treated with trastuzumab plus pertuzumab and a longer overall survival time.[14] An important observation found in this study was that some patients survived from 15 days to 14.7 years, i.e., despite treatment in advanced or metastatic stages, neoadjuvant and/or adjuvant therapy with trastuzumab may be associated with remission and late recurrence, which may explain the prolonged survival time.

This study was relevant, despite its limitations, mainly because it was conducted in a hospital for cancer patient care and exclusively serves SUS users, whose exposure to risk factors is more prominent and differentiated than those who have access to private health services. In addition, there are benefits in incorporating new therapies into Brazil's public health network for the treatment of women with metastatic HER2-positive breast cancer, impacting increased OS and better quality of life, even those diagnosed in more advanced stages. Perhaps the difficulty of accessing the public health service is responsible for the high rate of metastatic disease and a low life expectancy for these patients.

It is worth noting that innovative treatments with current drugs can significantly reduce costs for SUS bring about significant changes in therapeutic conduct, leading to adequate cancer treatment with excellent chances of healing. In addition, the costs of low-efficiency treatments may lead to long-term hospitalization, long-term incapacity; or even death, generating a significant financial burden on health institutions, suffering, and a high overall cost to the patient and their family.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Estimativa 2020: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2019.
2. Kang HJ, Kim JY, Lee NK, Lee JW, Song YS, Park SY, et al. Three-dimensional versus two-dimensional shear-wave elastography: associations of mean elasticity values with prognostic factors and tumor subtypes of breast cancer. Clin Imaging. 2018 Mar/Apr;48:79-85.
3. Nagini S. Breast cancer: current molecular therapeutic targets and new players. Anticancer Agents Med Chem. 2017;17(2):152-63.
4. Fisusi FA, Akala EO. Drug combinations in breast cancer therapy. Pharm Nanotechnol. 2019;7(1):3-23.
5. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019 Jan;321(3):288-300.

6. Ministério da Saúde (BR). Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC). Trastuzumabe para tratamento do câncer de mama avançado [Internet]. Brasília (DF): Ministério da Saúde/CONITEC; 2012. Available from: http://conitec.gov.br/images/Relatorios/2012/Trastuzumabe_caavancado_final.pdf

7. Ministério da Saúde (BR). Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC). Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Pertuzumabe para o tratamento do câncer de mama HER2-positivo metastático em primeira linha de tratamento associado ao trastuzumabe e docetaxel [Internet]. Brasília (DF): Ministério da Saúde/CONITEC; 2012. Available from: http://conitec.gov.br/images/Relatorios/2017/Relatorio_PertuzumabeTrastuzumabe_CA_Mama.pdf

8. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Apr;21(4):519-30.

9. Lima SGG, Brito C, Andrade CJC. O processo de incorporação de tecnologias em saúde no Brasil em uma perspectiva internacional. Ciênc Saúde Coletiva. 2019;24(5):1709-22.

10. Kalli S, Semine A, Cohen S, Naber SP, Makim SS, Bahl M. American Joint Committee on Cancer's Staging System for breast cancer, eighth edition: what the radiologist needs to know. Radiographics. 2018 Nov/Dec;38(7):1921-33. DOI: https://doi.org/10.1148/rg.2018180056

11. Bringolf L, Pestalozzi B, Fink D, Dedes K. Exploring prognostic factors for HER2-positive metastatic breast cancer: a retrospective cohort study in a major Swiss hospital. Swiss Med Wkly. 2016;146:w14393.

12. Suleman K, Mushtaq AH, Haque E, Badran AA, Ajarim D, Elashwah AM, et al. Trastuzumab, pertuzumab, and docetaxel as the first line for HER-2-positive metastatic breast cancer among Arabs. Breast Care. 2021;16(1):59-65.

13. Rahardja S, Tan RYC, Sultana R, Leong FL, Lim EH. Efficacy, patterns of use and cost of pertuzumab in the treatment of HER2+ metastatic breast cancer in Singapore: the National Cancer Centre Singapore experience. World J Clin Oncol. 2020 Mar;11(3):143-51.

14. Gamucci T, Pizzuti L, Natoli C, Mentuccia L, Sperduti I, Barba M, et al. A multicenter retrospective observational study of first-line treatment with pertuzumab, trastuzumab and taxanes for advanced HER2 positive breast cancer patients. Cancer Biol Ther. 2019;20(2):192-200.