ORIGINAL ARTICLE

Safety profile of dual blockade treatment with trastuzumab and pertuzumab in patients with her2+ metastatic breast cancer: real-world study

Perfil de segurança do tratamento de duplo bloqueio com trastuzumabe e pertuzumabe em pacientes com câncer de mama metastático her2+: estudo de mundo real

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ABSTRACT

Aims: This study analyzed the safety profile related to dual blockade with or without chemotherapy or hormone therapy in the treatment of HER2+ metastatic breast cancer. Adding potential variables associated with the risk of severe adverse events and possible implications of using biosimilars were analyzed, in a Brazilian referral hospital between October 2020 and April 2022. **Methods:** This is a real-world study conducted with 64 female participants divided into three groups: Dual Blockade, Dual Blockade + Chemotherapy, and Dual Blockade + Hormone Therapy. The analysis considered total treatment cycles and adverse events, which were classified by severity across groups. The association of social and clinical variables with adverse events was checked. The cycle-adjusted adverse events rate was calculated. Associations were estimated using Fisher's Exact test. The risk probability for variables predicting severe adverse events was calculated using the Odds Ratio, with a 95% Confidence Interval. **Results:** Diarrhea was the main adverse event identified. Overall, 33.9% of patients had some severe adverse events. The Dual Blockade + Hormone Therapy group showed the highest frequency of adverse events. White skin color and undergoing radiotherapy concomitant were associated with the risk of severe adverse events. Cycle-adjusted adverse events rates showed no significant difference between dual blockade with biosimilar and dual blockade with original trastuzumab. **Conclusion:** The safety profile identified was similar in the different groups analyzed and between dual blockade with biosimilar or original trastuzumab.

Keywords: Breast neoplasm, Biosimilar pharmaceuticals, Tastuzumab, Adverse event.

RESUMO

Objetivos: Este estudo analisou o perfil de segurança relacionado ao duplo bloqueio com ou sem quimioterapia ou hormonioterapia no tratamento do câncer de mama metastático HER2+. Foram analisadas variáveis potenciais associadas ao risco de eventos adversos graves e possíveis implicações do uso de biossimilares em um hospital de referência brasileiro entre outubro de 2020 e abril de 2022. **Métodos**: Este é um estudo de mundo real realizado com 64 participantes do sexo feminino divididas em três grupos: Bloqueio Duplo; Bloqueio Duplo + Quimioterapia; e Bloqueio duplo + Hormonioterapia. A análise considerou o total de ciclos de tratamento e eventos adversos, que foram classificados por gravidade entre os grupos. A associação de variáveis sociais e clínicas com eventos adversos foi verificada. A taxa de eventos adversos ajustada ao ciclo

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foi calculada. As associações foram estimadas usando o teste exato de Fisher. A probabilidade de risco para variáveis que preveem eventos adversos graves foi calculada usando a Odds Ratio, com um Intervalo de Confiança de 95%. **Resultados:** A diarreia foi o principal evento adverso identificado. No geral, 33,9% dos pacientes apresentaram algum evento adverso grave. O grupo de Bloqueio Duplo + Hormonioterapia apresentou a maior frequência de eventos adversos. A cor da pele branca e a realização de radioterapia concomitante foram associadas ao risco de eventos adversos graves. As taxas de eventos adversos ajustadas ao ciclo não mostraram diferenças significativas entre o bloqueio duplo com biossimilar e o bloqueio duplo com trastuzumabe originador. **Conclusões:** O perfil de segurança identificado foi semelhante nos diferentes grupos analisados e entre o bloqueio duplo com trastuzumabe biossimilar ou originador.

Palavras-chave: Neoplasia de mama, Produtos farmacêuticos biossimilares, Trastuzumabe, Evento adverso.

INTRODUCTION

Human epidermal growth factor receptor-2 (HER2) positive is a molecular subtype of breast cancer that affects nearly 20% of women with this type of cancer and is associated with a high relapse risk, greater tumor aggressiveness, and higher mortality rates compared to luminal A subtype[1-3].

In Brazil, dual blockade (BD) of trastuzumab and pertuzumab for HER-2-positive metastatic breast cancer (mBC) has been indicated. Trastuzumab is a monoclonal antibody that binds to subdomain IV of the HER-2 receptor and blocks its cleavage, stimulates cell-mediated cytotoxicity in an antibody-dependent manner, and inhibits HER-2-mediated mitogenic signaling in a ligand-independent manner[4]. Pertuzumab was developed after trastuzumab in order to optimize the effect and avoid resistance of cancer cells. It binds to subdomain II of the HER-2 receptor and blocks its heterodimerization in a ligand-independent manner[5].

Because they act on the same receptor, trastuzumab and pertuzumab have a complementary effect, producing a DB of activated HER-2 signaling[6]. In patients with early stage breast cancer, using DB associated with chemotherapy improved the overall pathological response rate[7]. In mBC patients, outcomes were also favorable, showing that DB associated with chemotherapy increased overall survival and progression-free survival[8].

As the costs of new cancer interventions increase, surveillance of real-world adverse events (AEs) and efficacy is also enhanced. Clinical trials restrict the population that will be treated, for example, to patients with best performance status and no metastasis, whereas this population is more diverse in the real world. Understanding outcomes in the general population generates several additional pieces of information for physicians, patients and policy-makers[9].

Few real-world studies have been found on the inherent safety profile of DB associated with chemotherapy or hormone therapy[10,11]. The aim of this study was to analyze the profile of AEs related to DB associated or not with chemotherapy or hormone therapy, the potential variables associated with the risk of severe AEs and the possible implications of the use of biosimilars, in a hospital that is a reference for the treatment of breast cancer in Brazil.

METHOD

Study design and setting

This is a real-world study conducted with participants with HER2+ mBC treated with DB, associated or not with chemotherapy or hormone therapy, in a cancer center treatment in Rio de Janeiro, Brazil.

Participants and eligibility criteria

The participants included in the study were women, over 18 years of age, undergoing treatment for HER2+ mBC and taking DB. Pregnant and breastfeeding participants were excluded.

The study was conducted with participants who started DB treatment in palliative therapy for HER2+ mBC between October 2020 and April 2022, even if they had only undergone one cycle of treatment. The period was defined based on the CLEOPATRA study[8], which was the main clinical study that informed the approval of DB (Herceptin® and Perjeta®) in participants with mBC. Participants were selected by collection data from the medical records on the institution's intranet, with pertuzumab use during the aforementioned period as the search criterion. All the information found was tabulated for further analysis of the medical records.

Variables and data sources

The following variables were surveyed to characterize the social profile: age, family history, skin color, and alcohol and tobacco consumption. For the clinical profile the following data were collected: presence of comorbidities, radiotherapy concomitant to drug treatment, Karnofsky Performance Scale (KPS) at diagnosis, hormone receptor status (progesterone and estrogen), menopausal status, disease progression, and use of hormone therapy. For the therapeutic profile were collected: start and end dates of DB use, total DB cycles, the biosimilar used in each cycle, and wheter there was associated chemotherapy or hormone therapy.

In order to minimize data loss, these variables were collected from both printed and electronic medical records. The collection was performed with the help of a form developed by the members of the research team. AEs were classified by study group as follows: DB; DB + Chemotherapy with taxane (DB+CTX); and DB + Hormone Therapy with anastrozole or tamoxifen (DB+HT). Analysis and classification as to severity was performed based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Where possible, AEs were confirmed by testing and reclassified (when necessary) according to all available information. Data were tabulated in a Microsoft Office Excel® 365 spreadsheet. AEs found in the study that were not described in the package inserts were grouped as "Other".

Statistical methods and ethical considerations

Data were analyzed using the Statistical Package for Social Sciences (SPSS) program, version 22.0 (IBM Co, A-monk, NY, USA). Absolute and relative frequencies were calculated for the categorical variables, and means and standard deviations were obtained for numerical variables. The association between the categorical varia-

bles was estimated using Fisher's Exact test. For the variables predicting severe AEs was calculated the Odds Ratio (OR), with 95% Confidence Interval (CI).

The frequencies corresponding to the AEs related to each manufacturer of trastuzumab used at the institution were compared. Due to the large number of manufacturers and the different number of cycles performed, an AEs rate adjusted by the number of cycles for each manufacturer was created in order to generate data that were proportionally comparable. The rate was generated using the formula shown below:

$$Adjusted\ AEs\ rate = \frac{number\ of\ a\ given\ AEs}{number\ of\ cycles\ of\ that\ brand}$$

AEs data were evaluated by infusion cycles. An association of the social and clinical variables with the identified AEs was made in order to verify if any of them had an influence on the safety profile.

This study was approved by the Research Ethics Committee of the institution, with CAAE number 60451122.5.0000.5274.

RESULTS

A total of 67 participants were eligible for the study, and three were excluded because they were breastfeeding, resulting in 64 participants analyzed. Social characteristics are described in Table 1. Their mean age at the time of diagnosis was 55 years (ranging from 37 to 81 years). Most participants had no family history of breast cancer (54.7%), were not white-skinned (50.0%), and did not smoke (73.4%) or drink alcohol (71.9%).

Regarding clinical data, 62.5% of participants were post-menopause, 70.3% had positive hormone receptors, and 48.3% were on hormone therapy. Comorbid conditions were identified in 62.5%, on which 75.0% had hypertension, 25.0% diabetes, and 47.5% obesity. There was a mean of 9 (±6) DB cycles and 87.5% of patients had not disease progression (Table 1).

Table 2 shows the corresponding frequency to AEs stratified by grade and divided by groups. A total of 248 AEs were reported, among which 33.9% were severe. Diarrhea was the most frequent. The DB+HT group showed the most AEs, with 56.5% of the total; its most frequent severe undesirable events were anemia and neutropenia. The DB+CTX group was the second in terms of the highest number of AEs, with 34.2% of the total, where hypersensitivity was the most frequent. The DB group had the lowest frequency of AEs, with 9.3% of the total. In this group, the most frequent severe AEs were neutropenia and febrile neutropenia. No statistically significant differences were identified in the analysis of the association of social and clinical data with AEs.

In this study, some AEs reported on the packaging were not observed, namely: fever, dry cough, leukopenia, thrombocytopenia, dysgeusia, increased lacerations, insomnia, and upper respiratory tract and nasopharyngeal infections. On the other hand, some AEs not reported on the package inserts were indeed observed, such as increased bilirubin, folliculitis and weight loss.

Table 1. Social and clinical data of patients with HER2+ metastatic breast cancer treated with trastuzumab and pertuzumab between October 2020 and April 2022. Rio de Janeiro, Brazil

Variable		n (%)
Age at diagnosis	Less than 60 years old	40 (62.5)
	60+ years old	24 (37.5)
	Mean (±Standard Deviation)	55 (11.4)
Family History	Yes	18 (28.1)
	No	35 (54.7)
	No information	11 (17.2)
Skin color	White	27 (42.2)
	Non-white	32 (50.0)
	No information	5 (7.8)
Smoking	Yes	14 (21.9)
	No	47 (73.4)
	No information	3 (4.7)
Alcoholism	Yes	13 (20.3)
	No	46 (71.9)
	No information	5 (7.8)
Menopause status	Pre	18 (28.1)
	Post	40 (62.5)
	No information	6 (9.4)
Comorbidities	Yes	40 (62.5)
	No	24 (37.5)
Radiotherapy concomitant	Yes	10 (15.6)
	No	54 (84.4)
KPS at diagnosis	100% – 80%	53 (82.8)
	Below 79%	11 (17.2)
HR status	Positive	45 (70.3)
	Negative	19 (29.7)
Hormone therapy	Yes	31 (48.4)
	No	33 (51.6)
Total DB cycles	Mean	9.2
	Standard Deviation	6.3
Disease progression	Yes	8 (12.5)
	No	56 (87.5)

Key: HR: Hormone Receptor; KPS: Karnofsky Performance Scale; DB: Dual Blockage.

Table 2. Adverse events stratified regarding grade and groups of patients with HER2+ metastatic breast cancer treated with trastuzumab and pertuzumab between October 2020 and April 2022. Rio de Janeiro, Brazil

Disorders by organic systems		DB+CTX (%)				DB (%)				DB+HT (%)			
		n (%)	G1 - 2	G3 - 4	NI	n (%)	G1 - 2	G3 - 4	NI	n (%)	G1 - 2	G3 - 4	NI
General and conditions of the application site	Fatigue	**5 (6.0)**	6.0	-	-	**3 (12.9)**	12.9	-	-	**16 (11.2)**	11.2	-	-
	Mucosa inflammation	**1 (1.2)**	1.2	-	-	**-**	-	-	-	**-**	-	-	-
	Asthenia	**5 (6.0)**	3.6	2.4	-	**1 (4.3)**	4.3	-	-	**9 (6.3)**	3.5	1.4	1.4
	Peripheral edema	**4 (4.8)**	1.2	-	3.6	**-**	-	-	-	**5 (3.5)**	1.4	-	2.1
Skin and subcutaneous tissue	Alopecia	**2 (2.4)**	1.2	1.2	-	**-**	-	-	-	**-**	-	-	-
	Rash	**1 (1.2)**	1.2	-	-	**-**	-	-	-	**1 (0.7)**	0.7	-	-
	Nail disorder	**-**	-	-	-	**-**	-	-	-	**1 (0.7)**	0.7	-	-
	Itching	**1 (1.2)**	1.2	-	-	**4 (17.2)**	17.2	-	-	**4 (2.8)**	2.8	-	-
Gastrointestinal	Diarrhea	**16 (18.8)**	15.4	2.4	1.2	**6 (25.8)**	25.8	-	-	**35 (24.5)**	13.1	0.7	0.7
	Nausea	**4 (4.8)**	4.8	-	-	**2 (8.6)**	8.6	-	-	**11 (7.7)**	7.0	0.7	-
	Vomiting	**1 (1.2)**	1.2	-	-	**-**	-	-	-	**3 (2.1)**	1.4	0.7	-
	Mucositis	**7 (8.4)**	7.2	1.2	-	**-**	-	-	-	**2 (1.4)**	1.4	-	-
	Constipation	**2 (2.4)**	2.4	-	-	**-**	-	-	-	**-**	-	-	-
Blood and lymphatic system	Neutropenia	**2 (2.4)**	1.2	1.2	-	**1 (4.3)**	-	4.3	-	**5 (3.5)**	-	3.5	-
	Anemia	**5 (6.0)**	6.0	-	-	**2 (8.6)**	8.6	-	-	**11 (7.7)**	4.2	3.5	-
	Febrile neutropenia	**2 (2.4)**	-	2.4	-	**1 (4.3)**	-	4.3	-	**-**	-	-	-
Nervous system	Peripheral neuropathy	**7 (8.4)**	8.4	-	-	**1 (4.3)**	4.3	-	-	**5 (3.5)**	2.8	-	0.7
	Headache	**1 (1.2)**	1.2	-	-	**1 (4.3)**	4.3	-	-	**5 (3.5)**	2.1	1.4	-
	Dizziness	**2 (2.4)**	1.2	-	1.2	**-**	-	-	-	**2 (1.4)**	0.7	-	0.7
Immune system	Hypersensitivity	**9 (10.6)**	-	10.6	-	**-**	-	-	-	**4 (2.8)**	-	2.8	-
Musculoskeletal and connective tissues	Myalgia	**-**	-	-	-	**-**	-	-	-	**3 (2.1)**	0.7	1.4	-
	Arthralgia	**2 (2.4)**	1.2	-	1.2	**1 (4.3)**	4.3	-	-	**7 (4.9)**	4.9	-	-
Respiratory, thoracic and mediastinal	Dyspnea	**1 (1.2)**	1.2	-	-	**-**	-	-	-	**1 (0.7)**	0.7	-	-
Metabolism and nutrition	Reduction in appetite	**2 (2.4)**	2.4	-	-	**-**	-	-	-	**6 (4.2)**	3.5	0.7	-
-	Other	**3 (3.6)**	1.2	1.2	1.2	**-**	-	-	-	**4 (2.8)**	0.7	0.7	1.4
	Total	**85 (100)**	**70.8**	**21.6**	**8.4**	**23 (100)**	**91.3**	**8.6**	**-**	**140 (100)**	**73.5**	**17.5**	**7.0**

Key: DB+CTX: Dual Blockade+Chemotherapy; DB: Dual Blockade; DB+HT: Dual Blockade+Hormone Therapy; NI: No Information ; G: Grade.

Statistical analysis was performed using Fisher's Exact test, associating toxicities with social and clinical variables.

Table 3 shows the variables that may be predictors of severe AEs. Statistically significant differences were identified for skin color and concomitant radiotherapy among patients who underwent DB treatment with original trastuzumab. White-skinned participants were at nine times higher chance of developing severe AEs than their not white-skinned counterparts. Participants undergoing radiotherapy concomitantly with drug treatment had seven times higher chance of developing AEs than those who did not.

Table 4 lists the AEs stratified by manufacturer. Diarrhea was the most fre-

quent AE in both biosimilars and the original drug. The most cycle-adjusted AEs reports were with the original drug (0.528), followed by manufacturers B, A and C (0.450, 0.424 and 0.192, respectively). When compared to the original, the biosimilars as a whole had not statistically significant difference in the frequency of AEs (p=0.052). When stratified analysis by the manufacturer of the biosimilar or original drug was performed, a significant difference was identified in the frequency of occurrence of AEs for one of them [p=0.052 (A), 0.383 (B), and 0.014 (C)].

Table 3. Analysis of the variables predicting severe adverse events in patients with HER2+ metastatic breast cancer treated with trastuzumab and pertuzumab between October 2020 and April 2022. Rio de Janeiro, Brazil

		SAEs with biosimilars					SAEs with original				
Variable		**Yes**	**No**	**OR**	**95% CI**	***p***	**Yes**	**No**	**OR**	**95% CI**	***p***
Age at diagnosis	<60 years old ≥60 years old	22 14	102 62	0.980	0.467-2.055	0.149	7 1	27 13	3.370	0.375-30.334	0.199
Family history	Yes No NI	14 16 6	52 85 27	1.430	0.645-3.170	0.109	7 - 1	17 18 5	-	-	-
Skin color	White Non-white NI	12 18 6	62 81 21	0.871	0.390-1.941	0.152	6 2 -	10 30 -	**9.000**	**1.559-51.949**	**0.010**
Smoking	Yes No NI	8 26 2	54 108 2	0.615	0.261-1.450	0.090	- 7 1	3 37 -	-	-	-
Alcoholism	Yes No NI	3 31 2	21 130 13	0.599	0.168-2.136	0.178	2 5 1	12 23 2	0.613	0.105-3.579	0.294
Menopause status	Pre Post NI	8 22 6	33 11 20	1.223	0.498-3.001	0.164	4 4 -	9 25 6	2.777	0.571-13.506	0.143
Comorbidities	Yes No	20 16	97 67	0.863	0.417-1.787	0.136	3 5	18 22	0.733	0.154-3.493	0.285
Radiotherapy concomitant	Yes No	5 31	29 135	0.750	0.269-2.095	0.175	3 5	3 37	**7.400**	**1.160-47.197**	**0.045**
KPS at diagnosis	100%-80% <79%	29 7	141 23	0.675	0.265-1.722	0.136	6 2	40 -	-	-	-
HR status	Positive Negative	23 13	116 48	0.732	0.342-1.563	0.111	4 4	31 9	0.290	0.060-1.398	0.099
Hormone therapy	Yes No	18 18	99 65	0.656	0.318-1.354	0.077	4 4	27 13	0.481	0.103-2.236	0.198
Disease progression	Yes No	6 30	30 134	0.893	0.341-2.337	0.187	1 7	6 34	0.809	0.083-7.819	0.417

Key: SAEs: Severe Adverse Events by cycle; HR: Hormone Receptor; KPS: Karnofsky Performance Scale; NI: No Information; OR: Odds Ratio; CI: Confidence Interval; significant p-value<0.05. The statistical analysis was performed using Odds Ratio associated with Fisher's Exact test.

Table 4. Adverse events in patients with HER2+ metastatic breast cancer treated with trastuzumab and pertuzumab between October 2020 and April 2022, stratified by manufacturer. Rio de Janeiro, Brazil

			Manufacturers of the biosimilars		
Adverse Events	**Original n (Rate)**	**Biosimilars n (Rate)**	**A n (Rate)**	**B n (Rate)**	**C n (Rate)**
Fatigue	6 (0.066)	18 (0.036)	7 (0.028)	10 (0.050)	1 (0.048)
Mucosa inflammation	-	1 (0.002)	-	1 (0.005)	-
Asthenia	1 (0.011)	14 (0.028)	5 (0.020)	9 (0.045)	-
Peripheral edema	1 (0.011)	8 (0.016)	1 (0.004)	7 (0.035)	-
Alopecia	1 (0.011)	1 (0.002)	1 (0.004)	-	-
Rash	-	2 (0.004)	2 (0.008)	-	-
Nail disorder	1 (0.011)	-	-	-	-
Itching	2 (0.022)	7 (0.014)	5 (0.020)	1 (0.005)	1 (0.048)
Diarrhea	11 (0.117)	46 (0.092)	22 (0.088)	23 (0.092)	1 (0.048)
Nausea	5 (0.055)	12 (0.024)	8 (0.032)	4 (0.020)	-
Vomiting	-	4 (0.008)	1 (0.004)	3 (0.015)	-
Mucositis	2 (0.022)	7 (0.014)	4 (0.016)	3 (0.115)	-
Constipation	-	2 (0.004)	2 (0.008)	-	-
Neutropenia	2 (0.022)	6 (0.012)	1 (0.004)	5 (0.025)	-
Anemia	5 (0.055)	13 (0.026)	11 (0.044)	2 (0.010)	-
Febrile neutropenia	-	3 (0.006)	1 (0.004)	2 (0.010)	-
Peripheral neuropathy	2 (0.022)	11 (0.022)	5 (0.020)	6 (0.030)	-
Headache	-	7 (0.014)	6 (0.024)	1 (0.005)	-
Dizziness	1 (0.011)	3 (0.006)	3 (0.012)	-	-
Hypersensitivity	1 (0.011)	12 (0.024)	8 (0.032)	3 (0.015)	1 (0.048)
Myalgia	-	3 (0.006)	1 (0.004)	2 (0.010)	-
Arthralgia	2 (0.022)	8 (0.016)	6 (0.024)	2 (0.010)	-
Dyspnea	-	2 (0.004)	1 (0.004)	1 (0.005)	-
Reduction in appetite	3 (0.033)	5 (0.010)	4 (0.016)	1 (0.005)	-
Others	2 (0.011)	5 (0.010)	1 (0.004)	4 (0.020)	-
Total	**48 (0.528)***	**200 (0.400)***	**106 (0.424)**	**90 (0.450)**	**4 (0.192)**

Cycle-adjusted adverse events rate = Adverse events/Treatment Cycles

* *p*=0.052 (Fisher's Exact test).

DISCUSSION

A safety profile was identified in Brazilian women with HER2+ mBC treated with DB. Overall, the results found are similar to those identified in pivotal studies, although it was possible to observe other AEs that had not been previously reported. The paired analysis between the use of DB with the biosimilar and original drugs pointed to a similar safety profile.

The study population was women with HER2+, mostly non-aging and hormone receptor positive. These population characteristics are very similar to those found in the study by Lee *et* al.[12], who identified 70% of non-aged participants with mBC and 54% with hormone receptor positive.

Diarrhea was the AE most frequently found in the study, similar to previous findings. In the CLEOPATRA study[8], diarrhea was the most incident AE in the DB+CTX group and the third most reported in the DB group. The group that had the highest frequency of AEs was DB+HT, which also performed the highest number of cycles. According to Thanarajasinga[13], some AEs such as diarrhea and mucositis remain constant throughout the treatment. Consequently, the more cycles, the greater the tendency for AEs.

It is worth noting that this was the first study that aggregated groups considering the use of DB+HT, since the intention was to verify the existence of a potential influence of hormone therapy on the safety profile of participants undergoing DB. However, our findings did not identifying any possible association.

Although the DB+HT group had a higher number of cycles, it was this group that had more severe AEs (17.5% versus 21.6%). In a multicenter study conducted by Hua *et* al.[14], it was observed that participants using trastuzumab with hormone therapy had a lower frequency of severe AEs than those on trastuzumab with chemotherapy (3.1% versus 51%). The difference found between the groups in our study was smaller, which may be related to the limited number of participants and the fact that the incorporation of pertuzumab for the treatment of patients with mBC in public hospitals had been recent in Brazil.

No cardiotoxicity profiles associated with the biosimilars or the original drug were identified in this study. However, some limitations related to institutional procedures need to be considered. At the researched institution, echocardiography is performed before the start of treatment and is repeated only in case of clinical signs of cardiotoxicity, making it impossible to monitor early impacts on left ventricular function in participants. Consequently, it cannot be claimed that the study participants did not have any type of injury indicative of cardiotoxicity.

White-skinned participants were at higher chance of developing AEs toxicities when compared to their non-white-skinned counterparts. According to McCollum *et* al.[15], this difference may be due to changes in tumor biology between different racial groups, which result in differences in tumor aggressiveness and ability to respond to therapy. Han *et* al.[16] found no significant differences in the frequencies of severe AEs between Caucasian and Afro-American groups. However, the Afro-American participants had a lower incidence of AEs than Caucasian group in the first cycle.

Participants undergoing radiotherapy concomitant with drug treatment had a higher chance of developing severe AEs

compared to those who did not undergo radiotherapy. In 2022, Latrèche *et* al.[17] presented some AEs related to chest radiotherapy, with cardiac, hematological and dermatological events among them; which are also related to DB treatment. Therefore, a synergistic effect may have occurred between radiotherapy and drug therapy, culminating in an increased risk of AEs.

The analysis of AEs by manufacturers, original drugs and biosimilar was performed based on the impossibility imposed by Brazilian treatment institutions of having no control over the purchase of drugs used in DB. Ordinance 73/2013[18] incorporated the centralized purchase process of trastuzumab, which is carried out by the Ministry of Health, distributing the drug to the State Departments of Health. Consequently, it is possible for the same patient to receive the original trastuzumab or biosimilar from different manufacturers throughout their treatment.

Only one of the biosimilars showed a significant difference from the original drug and the manufacturer in question. However, the number of cycles with this manufacturer was fewer than with the others. Thus, this difference may have been due to the low exposure rate of patients to this biosimilar. Regarding the other manufacturers alone and the biosimilars as a group, no significant differences were observed between the frequency of AEs in the biosimilar and original drug groups, suggesting that using a biosimilar is as safe as the original drug. Several studies by Bernat-Peguera and Suppan[19,20] show no significant differences in the frequency of AEs between DB treatment with biosimilar or original trastuzumab, thus ratifying the findings of this study.

The study had limitations inherent to the evaluation of real-world studies and due to the fact that pertuzumab was recently incorporated into the Brazilian Public Health System. Despite the small number of participants, the brief follow-up time and the disproportion in the use of the different biosimilars compared to the original drug, this is the first Brazilian study on the topic and it was possible to obtain important data on the safety profile that can be used for clinical decision-making.

CONCLUSION

The results of the current study indicated that diarrhea is the main AE affecting patients with HER2+ mBC treated with DB, combined or not with CTX or HT. In addition, previously unidentified AEs such as increased bilirubin, folliculitis and weight loss were detected. Patients with white skin and undergoing radiotherapy concomitant were identified as having a higher chance of developing severe AEs. The safety profile was similar in the groups, regardless of trastuzumab manufacturer, suggesting that trastuzumab biosimilar associated with pertuzumab is as safe as DB with the original trastuzumab.

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