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Original Article

COST-EFFECTIVENESS ANALYSIS OF TRASTUZUMAB IN THE TREATMENT OF METASTATIC BREAST CANCER

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ABSTRACT

Objective: To perform a cost-effectiveness analysis of pharmacological treatments for MBC in the context of the Brazilian Unified Health System (Sistema Único de Saúde - SUS) by comparing the drugs docetaxel and paclitaxel in isolation and in combination with trastuzumab.

Methods: The results for each treatment were simulated using a Markov model and a hypothetical cohort of 1000 women aged 50 years diagnosed with MBC with overexpression of HER2. The progression of MBC was simulated for 48 months and the transitions between health states occurred monthly. A sensitivity analysis was performed. The discount rate considered was 5% per year.

Results: The addition of trastuzumab allowed a gain of eight to ten months in the average lifespan after a four-year treatment. The increased threshold allows the increased use of trastuzumab combined with paclitaxel in the treatment of MBC. The combination of trastuzumab with docetaxel and paclitaxel achieved an effective gain in the survival of patients with MBC, and the average survival time doubled compared with monotherapy.

Conclusion: Considering that the costs per quality-adjusted life year (QALY) of these treatment strategies were below the threshold of 3 times the per capita GDP recommended by WHO, both strategies can be considered cost-effective.

Keywords: Metastatic breast cancer, Cost-effectiveness, Trastuzumab.

INTRODUCTION

Cancer is a major public health problem in developed and developing countries. The World Health Organization (WHO) estimates that approximately 13% of all deaths are due to cancer, and the tendency is to increase by 2030, particularly in middle- and low-income countries [1].

In Brazil, cancer and cardiovascular diseases have been the leading causes of death in recent years. These diseases are associated with an aging population resulting from intense urbanization processes and from actions to promote and restore health [2, 3]. According to the National Cancer Institute (Instituto Nacional do Câncer–INCA), in 2014, breast cancer will be the cancer with the third highest incidence after non-melanoma skin cancer and prostate cancer [2, 4].

Although the incidence rates remain high in the population, breast cancer may have a good prognosis if diagnosed and treated early. Increased surveillance of breast cancer and the use of systemic therapies have increased average survival in developing countries [5- 7].

In turn, metastatic breast cancer (MBC) is an advanced stage of the disease in which the disease has spread beyond the original organ. It is considered an aggressive disease and there is growing evidence that its prognosis is poor. The objective of current treatments for MBC is to relieve symptoms, prolong survival, and maintain a good quality of life with minimal adverse events (AEs). The drug therapy of choice usually involves trastuzumab (TRA) (Herceptin®, Roche) in combination with other drugs.

According to the CONITEC-08 report [8], the available studies have not confirmed whether the use of trastuzumab has any impact in the treatment of breast cancer that is characterized by the over expression of HER2++ [9]. Nevertheless, Ordinance No. 18 of July 25, 2012 incorporated the use of this drug and demanded some conditions, including price reduction, performance of a molecular test by fluorescence in situ hybridization (FISH) to confirm the over expression of HER2+ in tumors with immune histochemical expression having one or two plus reactions, the availability of 100-mg and 150-mg drug presentations, monitoring of clinical outcomes in hospitals specializing in oncology, and compliance with the diagnostic and therapeutic guidelines issued by the Ministry of Health [10]. On another CONITEC document, the use of trastuzumab in combination with paclitaxel or docetaxel is indicated as the first-line treatment for patients with tumors that over express HER2, i. e., for patients who have not undergone chemotherapy for metastatic diseases.

The objective of this study was to evaluate the cost-effectiveness of treatments involving the drugs trastuzumab+paclitaxel, paclitaxel, trastuzumab+docetaxel, and docetaxel for metastatic breast cancer in the context of the Brazilian Unified Health System (Sistema Único de Saúde - SUS).

MATERIALS AND METHODS

A Markov model of health state transitions that represent the progression of metastatic breast cancer over mensal cycles was developed to estimate the costs and benefits of the therapeutic approaches to the disease. The SUS perspective was used to estimate the costs, and the benefits were measured in quality-adjusted life years (QALYs). The time horizon was 48 months. The cost comparison between the drugs was conducted using the incremental cost-effectiveness ratio (ICER). A discount rate of 5% was applied to the costs.

Decision analysis software was used for the analysis of cost-effectiveness [11]. A hypothetical cohort of 1, 000 female individuals was designed. These individuals were 50 years of age and had diagnoses of metastatic breast cancer with HER2 over expression. The probabilities of transition among the states of health in metastatic breast cancer are listed in table 1.

The disease's progression was modeled using 3 health states according to Athanasakis *et al.* [32]. The Markov states progressed monthly and included primary disease and metastasis.

According to a CONITEC report [8], trastuzumab in combination with docetaxel or paclitaxel is recommended as a first-line treatment for patients with metastatic disease [8, 14, 34]. By contrast, the treatment protocol for breast cancer established by INCA

recommends palliative chemotherapy for metastatic disease [15, 16]. If the disease is HER2++, chemotherapy associated with trastuzumab should be used as the first-line treatment until maximum disease stabilization is achieved. Pre-medications are used to avoiding or decrease certain undesirable effects of the infusion. The drugs commonly used before chemotherapy for this indication are dexamethasone (10 mg, IV), cimetidine (300 mg, IV), and pheniramine (50 mg, IV) [17].

Table 1: Probabilities of transition among the states of metastatic breast cancer progression

Medications	Time (months)	Hazard ratio	Probability	Source
Trastuzumab + Docetaxel				
Primarydisease	26	0.026058	0.025396	[12]
Metastasis	1.3	0.53319	0.347765	[12]
Docetaxel				
Primarydisease	22.6	0.03067	0.029758	[12]
Metastasis	1	0.693147	0.409384	[12]
Trastuzumab+Paclitaxel				
Primarydisease	22.1	0.031364	0.03041	[13]
Metastasis	6.9	0.100456	0.091286	[13]
Paclitaxel				
Primarydisease	18.4	0.037671	0.036303	[13]
Metastasis	3	0.231049	0.187685	[13]

Source: Developed by the authors

The estimated cost of these drugs was based on the average price per drug vial and duration of treatment. The cost of treatment was calculated for women with weight of 55 kg, height of 1.60 m, and body surface of 1.563 m^2(Body surface area was calculated using the formula 0.007184 x height $(cm)^{0.725}$ x $weight^{0.425}$).

For treatment with the combined use of paclitaxel and trastuzumab, Gasparini et al. [18] considered the performance of the following tests 28 days before infusion to be essential: physical examination, complete blood count, serum biochemistry, electrocardiography, echocardiography for assessment of left ventricular ejection fraction (LVEF), tumor evaluation on X-ray and computed tomography. During treatment, the authors chose to conduct clinical and biochemical tests and routine chest X-ray before each cycle. The evaluation of LVEF using echocardiography was performed every 12 weeks after the clinical onset of cardiac symptoms [17, 18]. The evaluation of hematological and non-hematological toxicity was performed every two weeks [17]. In the most severe cases, such as in congestive heart failure, the standard treatment was recommended together with reduction or discontinuation of chemotherapy [17]. In the case of fever or severe neutropenia, filgrastim 5 g/kg was used daily intravenously until the absolute neutrophil count was above 10, 000/mm^3 [18].

A literature review was conducted to determine treatment effectiveness. The search included the studies published until 2011 that investigated the effectiveness of drugs used to treat metastatic breast cancer patients over expressing HER2. The data derived from these studies were included in the model. Patients aged 50 years, for whom the presence of HER2++ was confirmed using immune histochemistry or FISH, and those with locally advanced MBC, were considered eligible for participation in the study. The patients had normal hematologic, liver, and kidney functions and their LVEF was evaluated using echocardiography. Moreover, the patients could have received up to one chemotherapy drug for metastatic disease. Patients with a Karnofsky index below 60%, lifespan of less than 3 months, or inadequate hematologic, kidney, liver, or heart function (LVEF <50%) were excluded [24, 25]. The Karnofsky index is a scale used to classify patients as to their functional capacity. This scale can be used to compare the effectiveness or effects of different treatments and to establish the patient's prognosis. The lower the Karnofsky score is, the worse the survival is for most severe diseases [35]. Patients with advanced metastatic disease or who had previously received anthracycline or taxane, those with significant sensory or motor neuropathies, and those with past or active heart disease were excluded [25].

Table 2: Model probabilities for the use of trastuzumab combined with paclitaxel or docetaxel and for monotherapy with paclitaxel or docetaxel

Model parameters	Base-case value (%)	Variation used in the sensitivity analysis (%)	Source
Response rate, HER2-positive			
PLA	27	19–35	[26, 27]
TRA+PLA	54	45–63	[26, 27]
Response rate, HER2-negative	38	26–55	[26, 27]
Monthly probability of disease progression, HER2-negative			
Responsive state	9	4–14	[28]
Unstable disease	12	7–17	[28]
Relative increase in the rate of disease progression, HER2-positive, PLA monotherapy	1.5	1.0–2.0	[29]
Relative decrease in the rate of disease progression due to TRA, HER2-positive	0.8	0.5–1.0	[28]
Monthly probability of death as a result of progressive disease	5	2–10	[28]
Prevalence of HER2-positive disease	25	15–30	[29]
Demographic characteristics of the population			
Average age (years)	53		[12]
Average duration of the primary disease (months): TRA+DOC	26.6		[12]
Average duration of the primary disease (months): DOC	22.6		[12]
Average duration of metastatic disease (months): TRA+DOC	1.3		[12]
Average duration of metastatic disease (months): DOC	1.0		[12]
Utility values			
Disease-free survival	0.74		[30]
Disease progression	0.44		[30]

Source: Developed by the authors

In this model, the data obtained from the study conducted by Marty et al. [12] and Gasparini *et al*. [18] were used. For the evaluation of tumor response rates, the minimum treatment period was 12 weeks.

The response rates and the study references are listed in table 3. For several drugs, multiple outcome measures were found. In these cases, the best response rate was included in the model, and the worst rate was included in the sensitivity analysis. The adverse effects that were reported for each drug were not considered.

The outcomes of interest selected in the studies evaluated included overall response rate (ORR), progression-free survival (PFS), and time to progression (TTP) [12, 18]. The duration of response was calculated by counting the number of days from the date of the objective response until the first date of disease progression. TTP was calculated as the number of days between the date of the first infusion and either the date of disease progression or the date on which the patient was free of progression. PGS was calculated from the date of enrollment until the date of death from any cause. [18].

Table 3: Outcomes of interest incorporated into the Markov model

Parameters	Drug therapy		Source
	TRA+DOC	DOC	
ORR (%) (% C. I.)	61 (50–71)	34 (25–45)	[12]
CR (%)	7	2	[12]
PR (%)	54	32	[12]
SD (months)	31.2	22.7	[12]
TTP (months)	11.7	6.1	[12]
DR (average, in months)	11.7	5.7	[12]
SD (%) (% C. I.)	27 (18–37)	44 (33–54)	[12]
Parameters	**Drug therapy**		**Source**
	PLA	PLA+TRA	
CR (%)	13.8	21.7	[18]
PR (%)	43.2	53.3	[18]
DR (%) (% C. I.)	24.1 (32.3–62.6)	18.3 (73.1–95.8)	[18]
TTP (%)	18.9	6.7	[18]
ORR (%) (% C. I.)	57 (43.2–69.8)	75 (62.1–85.3)	[18]

Source: Developed by the authors. (ORR–overall response rate; CR–complete response; PR–partial response; SD–stable disease; TTP–time to progression; DR–duration of response; CI–confidence interval)

Evaluation of overall survival and time to progression

The clinical trials evaluated served as the basis for this study and their data were extrapolated with respect to disease progression. Different scenarios for the Markov transition probabilities were createdto replicate the results accumulated in the few years in which the clinical trial was performed. It is recognized that exact reproduction is not possible but its approximate calculation is feasible. According to Garrison et al. [25], from the sixth year onwards, the annual probability of transition to metastasis and death were considered equal in all segments of the model. The calculation was performed by estimating the risk (hazard rate) as HD = –ln (0.5)/average time, and this value was transformed into a probability according to the formula P=HD/(1+HD).

Table 4: Utility values of the base-case (stable MBC during treatment without toxicity) and gains in utility value and associated decreases in health state

Utility values	Base-case value	Source
Base case stable disease without toxicity	0.715	[30]
Response totreatment	0.790	[30]
Diseaseprogression	0.443	[30]
Adverse effects		[30]
Febrileneutropenia	0.565	[30]
Diarrheaandvomiting	0.612	[30]
Stomatitis	0.564	[30]
Fatigue	0.600	[30]
Alopecia	0.601	[30]

The time frame applied was 48 months [13]. The costs and benefits were discounted by using a rate of 5% as suggested in the Methodological Guidelines for Assessment of Economic Studies [10]. Table 6 summarizes the parameters used in the model.

The utility value takes into account the quality of life of the patient in the different health states observed along the course of the disease. The adverse effects evaluated were fever, neutropenia, stomatitis, diarrhea/vomiting, fatigue, hand-foot syndrome, and alopecia. Stable disease undergoing treatment had a utility value of 0.72 with a corresponding gain of 0.07 in cases where response to treatment was observed and a decrease of 0.27 in cases of disease progression. The utility values of the ART+DOC combination were obtained from Lloyd et al. [30] and are presented in Table 5 along with the utility values associated with the adverse effects of interest.

RESULTS

The results for each treatment were simulated using a hypothetical cohort of 1000 women aged 50 years diagnosed with MBC and with HER2 over expression (immune histochemistry score of 3+ or FISH-positive results). At the end of each cycle, the women moved between these health states as determined by the respective probabilities of treatment and transition. The model simulated MBC progression after treatment for a total period of 48 months. M.o.rtality in the state of progressive disease depended on the initial treatment or the HER-2++ status. Death from metastatic breast cancer was only possible among women with disease progression.

The addition of trastuzumab to paclitaxel or docetaxel more than doubled the probability of survival at the end of 48 months, with this probability going from 8.6% to 19.1% and from 12% to 25.4%, respectively. The plot below shows the probability of survival for each treatment.

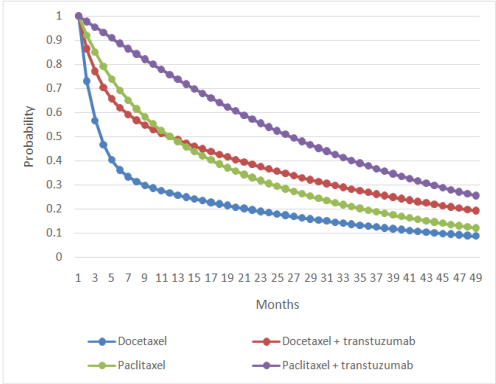

Fig. 1: 1Survival probability curve for metastatic breast cancer for each treatment

Table 5: Model parameters per cycle and patient

Effectiveness	Utility value	PDP	PD	CTX cost (US$)	Pre-CTX cost (US$)	Pretreatment exam cost (US$)	Exam cost during treatment (US$)	Palliative treatment cost (US$)	Source
Paclitaxel									
ORR: 57% (13.8% CR/ 43.2% PR)	Stable = 0.72 Progression = 0.45 Death = 0	0.036303	0.018765	49.70	1.42	180.52	11.52	851.65	[18]
Docetaxel									
ORR: 34% (2% CR/32% PR)	Stable = 0.72 Progression= 0.45 Death = 0	0.029759	0.409384	223.60	0.19	17.79	76.88	851.65	[12]
Paclitaxel									
ORR: 75% (21.7% CR/ 53.3% PR)	Stable = 0.72 Progression = 0.45 Death = 0	0.03041	0.091286	631.10	1.42	180.52	11.52	851.65	[18]
Docetaxel									
ORR: 61% (7% CR / 54% PR)	Stable = 0.72 Progression = 0.45 Death = 0	0.02539	0.347765	2503.62	0.19	17.79	76.88	851.65	[12]

Source: Calculated by the authors using data from 'Compras Net' for each bid [22]. The period of validity for the bids was 2014.* *The cost was calculated based on the lowest price found. The treatment times were 48 weeks The U. S. dollar exchange rate on 04/09/2014 was R$2.24 [23].

The follow-up data were extracted from [20, 21], (ORR- overall response rate; CR – complete response; PR- partial response; CTX- chemotherapy; PD – probability of death; PDP - probability of disease progression)

An incremental cost-effectiveness analysis was performed by ranking the strategies evaluated in order of increasing cost. The comparisons were made for the following drug therapies for metastatic breast cancer: trastuzumab combined with either docetaxel or paclitaxel, docetaxel alone, and paclitaxel alone.

Sensitivity analysis

The extent of change in the results caused by systematic variation of the estimates and assumptions was tested using sensitivity analysis. The following variables of each alternative under analysis were modified: (a) cost of chemotherapy; (b) probability of cancer progression, and (c) probability of death after disease progression.

The impact of these variables on the univariate analysis is shown in the tornado diagram below.

Source: Developed by the authors; *Quimio=Chemo; Morrer = Death

Table 6: Cost effectiveness of the treatment strategies for metastatic breast cancer (MBC)

	Strategy	Cost (US$)	Incremental cost (US$)	Effect (QALY)	Incremental effect (QALY)	ICER (US$/QALY)
All						
1	Docetaxel	2, 510.89		7.09		
2	Trastuzumab + Docetaxel	12, 184.47	9, 673.59	13.27	6.18	1, 565.5
3	Paclitaxel	39, 374.30	27, 189.83	11.41	–1.86	**Dominated**
4	Trastuzumab+Paclitaxel	62, 468.05	50, 283.57	17.27	4.00	12, 573.61
Non-dominated						
1	Docetaxel	2, 510.89		7.09		
2	Trastuzumab+Docetaxel	12, 184.47	9, 673.59	13.27	6.18	1565.49
4	Trastuzumab+Paclitaxel	62, 468.05	50, 283.57	17.27	4.00	12, 573.61

Source: Developed by the authors; *ICER=incremental cost effectiveness ratio

The variables with the greatest impact were the probability of progression for treatment with docetaxel and the addition of trastuzumab to paclitaxel. Nevertheless, neither of the two variables changed the ranking of the therapeutic alternatives evaluated.

Moreover, the accessibility curve indicated no differences between the different treatment strategies. The increased threshold enables the increased use of trastuzumab combined with paclitaxel in the treatment of MBC.

DISCUSSION

The treatment with paclitaxel was discarded because of its dominance in relation to the treatment with trastuzumab combined with docetaxel. The former proved to be more expensive and less effective. The incremental cost-effectiveness ratios (ICERs) of the remaining strategies were recalculated using cost-effectiveness analyses.

The addition of trastuzumab to paclitaxel or docetaxel introduced an effective gain in the quality of life of the patient. In turn, the increased cost of adding trastuzumab to these two drugs was approximately five-fold for each combination compared with a gain in the quality of life of approximately one-third. I

mportantly, following the recommendations of the World Health Organization [1], all treatment strategies can be considered cost-effective because they were below the acceptability threshold of up to 3 times the national per capita GDP value, which is approximately

R$ 20, 000.00/Qaly (The GDP per capita in Brazil was R$ 22, 402 in the first semester of 2012 [30]).

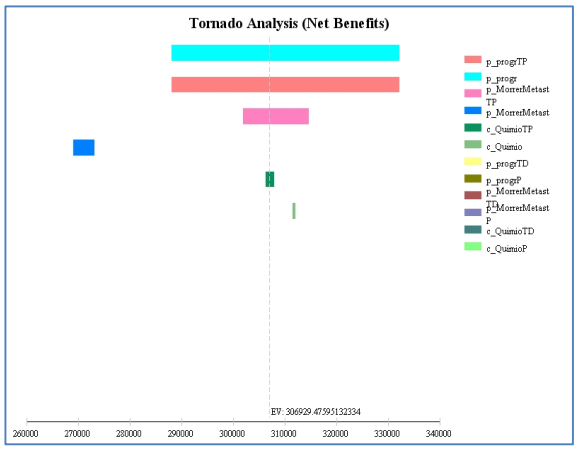

Fig. 2: Univariate sensitivity analysis

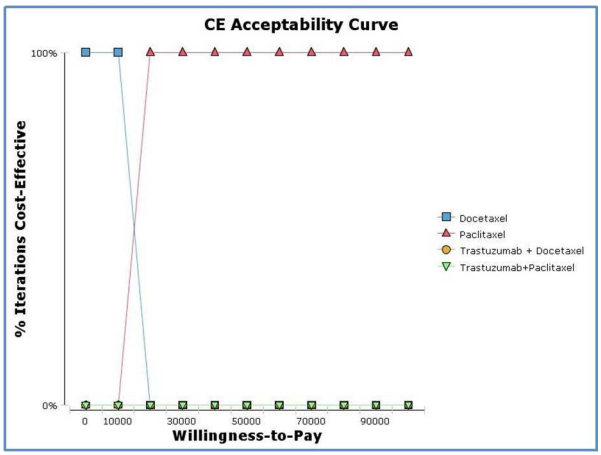

Fig. 3: Acceptability curve

Other studies that have used economic models to evaluate the impact of treatment with trastuzumab and other drugs have reached similar conclusions. Athanasakis et al. [32] performed a cost-effectiveness analysis comparing DOC and DOC+TRA in the Greek health system. Both DOC and TRA cost € 5.95/mg. The average total costs were € 36, 442.04 for TRA and € 27, 323.98 for DOC. The analysis showed that the ICER was € 37, 759 and € 61, 323 for each year of life or each QALY, respectively. According to the authors, the addition of TRA to DOC as the first-line treatment for HER2-positive MBC is a cost-effective intervention.

Poncet et al. [33] analyzed the use of TRA combined or not with PLA in 45 patients diagnosed with MBC and with average age of 51 years The average overall survival was 17 months longer in the TRA+PLA group compared with the PLA group (29 months versus 12 months). The average rate of progression-free survival was 12.2 months longer in the group treated with the combination therapy (19 months versus 7 months) and the average cost of general care was € 33.271 per patient in the TRA+PLA group compared with € 11.191 per patient in the PLA group.

The additional cost per year of life saved expressed as the increase in cost-effectiveness was € 15, 370 in 2002. The authors concluded that the additional associated cost was accessible to the European health system and justified the recommendation for the use of this therapy in the subpopulation with HER2 over expression.

Garrison et al. [25] studied a dynamic model embedded in an epidemiological model, simulating a cohort with an annual number of patients at risk of developing BC and MBC in the US. According to these authors, treatment with trastuzumab decreased the incidence of MBC. Therefore, its future use will be much more extensive. The estimated ICER was US$ 35.590/QALY with a discounted total of 432, 547 QALY gains.

Norum et al. [36] obtained results completely different from those of the other studies cited, wherein the addition of trastuzumab to the therapy was not cost-effective in patients with MBC and HER2 over expression. The authors evaluated costs related to the disease in 2003 in Norway. The measures of effectiveness were life years (LY) and quality of life (QOL) gains. The acquired LY ranged between 0.3 and 0.7 years. The average cost per patient treated was € 4, 196 and the cost per year of life saved ranged between € 63, 137 and € 162, 417, depending on the survival gains and the discount rate used. This evaluation indicated that TRA was not effective in the treatment of MBC. However, if the drug costs had been lower in 2003 or if the treatment yielded an improvement in patient survival, this conclusion could be different.

CONCLUSION

It is estimated that in 2014, there will be approximately 500, 000 new cases of cancer in Brazil. The INCA has estimated that breast cancer is the cancer with the third highest incidence with 53, 000 new cases, and it is the most common type of cancer in almost all regions of Brazil [2, 37]. The clinical course of metastatic breast cancer and this heterogeneity is due to the large differences in tumor growth rate and responsiveness to systemic therapy. Increased survival has been observed using first-line treatments in patients with breast cancer. For these patients, an extended lifespan free of disease can be reached and the chance of success is associated with a complete response after the first-line treatment.

In the model developed, the addition of trastuzumab to paclitaxel and docetaxel introduced an effective gain in the survival of patients with MBC. In both cases, the average survival period doubled relative to monotherapy. Moreover, considering that the costs per QALY of these treatment strategies were below the threshold of 3 times the per capita GDP recommended by WHO, both strategies can be considered cost-effective. However, given that the addition of trastuzumab to paclitaxel was more effective, this therapeutic regimen is the best choice according to the methodology used in this study.

The models of MBC treatment based on Markov chains that simulate the natural development of MBC vary widely internally, although these models usually use the same clinical trials as a reference for defining the basic parameters to be used in the model. No previous model had analyzed the use of paclitaxel and docetaxel in isolation or the use of these drugs in combination with trastuzumab. However, the results presented here insupport the use of combined therapies because they are more cost-effective and greatly increase patient survival.

The main limitation of the present study was the need to estimate the response data at the completion of drug therapy. Mitigation of this limitation was attempted using sensitivity analysis, which varied some parameters. In addition, the transition probability between the disease states as well as the effectiveness and utility values were obtained from the literature, but these results can diverge from the national reality in absolute terms. One factor that may influence the response to MBC treatment and, consequently, change the relationship between drug costs and effects is drug prices in the Brazilian market.

In addition, no Brazilian studies have used economic models to perform a clear comparison of four different drug therapies as was conducted in the present study. Therefore, our study is considered original and innovative.

Considering the significant resources allocated to fund this novel drug therapy and the increased pressure on health budgets, economic assessments are necessary to compare their health effects with their costs. In view of the lack of mathematical models that take into account patient survival and the lack of concrete effectiveness data for drug therapies used in MBC, additional clinical studies and economic assessments on this topic are essential.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the content of this article.

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