Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 7, 2015

Original Article

TRASTUZUMAB IN METASTATIC BREAST CANCER: SYSTEMATIC REVIEW OF COST-EFFECTIVENESS ANALYSES

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Received: 24 Mar 2015 Revised and Accepted: 08 May 2015

ABSTRACT

Objective: To conduct a systematic review of cost-effectiveness analyses of trastuzumab in patients with metastatic breast cancer overexpressing human epidermal growth factor receptor 2.

Methods: A systematic review for the years 1998 to 2013 was conducted. A survey of the scientific literature was performed using six electronic databases, two search tools on the internet and a manual search of references using search strategies for each database. The selected studies were assessed for quality according to specific methodology. Data analysis was performed by converting the costs and by observations made from the incremental cost-effectiveness ratios of trastuzumab.

Results: From a detailed analysis of 521 retrieved articles, 13 articles were selected for this review. The treatment regimens adopted for cost-effectiveness were varied. Eight studies compared treatment with trastuzumab as first line for metastatic disease, and five studies compared treatment with trastuzumab as the second line. All the studies were using trastuzumab as second-line treatment was not considered a cost-effective intervention. The analyses used different thresholds to determine whether treatment with trastuzumab was cost-effective as well as to determine differences in modeling costs, outcomes and treatment patterns.

Conclusion: The use of trastuzumab, alone or combined, was cost-effective as first-line treatment. Differences were found in the quality of the included studies. Conducting new cost-effectiveness analyses of trastuzumab in metastatic breast cancer is required, in alliance with political, social and administrative factors, to help decision makers concerning its incorporation.

Keywords: Trastuzumab, Cost effectiveness, Breast cancer, Systematic review.

INTRODUCTION

According to estimates of the National Cancer Institute (Instituto Nacional do Câncer José Alencar Gomes da Silva-INCA), in 2014 and 2015, there will be approximately 576,000 new cases of cancer, of which 57,000 will be cases of female breast cancer. Breast cancer is the most frequent neoplasm in women from the Southeast, South, Midwest and Northeast regions of Brazil and the second most prevalent neoplasm in the North region, where cervical cancer is the leading neoplasm [1].

Approximately 30-50% of patients diagnosed in the initial stages will develop a metastatic disease. In this incurable phase of the disease, the therapies aim to prolong the survival and provide palliative control of symptoms [2]. The over expression of human epidermal growth factor receptor 2 (HER2) occurs in approximately 25% of all cases of breast cancer and is associated with lower disease-free interval and survival [3]. Trastuzumab, a monoclonal antibody directed at HER2, has been increasing the response, progression-free survival and/or overall survival rates in metastatic breast cancer [2, 4, 5].

Many countries have economic pressures from their healthcare systems and society to provide coverage for monoclonal antibodies due to their high prices [3]. Treatment with trastuzumab is unlikely to be affordable by most patients, unless it is covered by the public or private healthcare system [6]. The Ministry of Health has incorporated trastuzumab in the Coverage table of the Sistema Único de Saúde (SUS), the Brazilian Unified Health System, for initial and advanced breast cancer, excluding the metastatic phase [7, 8]. The main issues regarding the cost-effectiveness of trastuzumab use in metastatic breast cancer have remained unanswered in the literature, because data used to support these demands are dispersed across different studies from different organizational contexts. The studies found are often small-scale and methodologically flawed and refer to non-controlled clinical trials, making them unsuitable for formal meta-analyses [6].

It is important to consider that the successful development of a systematic review generates a reliable estimate of the effect of the intervention studied [9]. Therefore, a systematic literature review was performed to identify relevant articles concerning the cost-effectiveness of trastuzumab for metastatic breast cancer in patients with over expression of HER2 compared with other chemotherapy regimens adopted. The present systematic review secondarily aimed to add supporting information to future discussions on the cost-effectiveness ratio of trastuzumab and subsequent incorporation of trastuzumab by SUS for the treatment of metastatic breast cancer.

MATERIALS AND METHODS

Study design

A systematic review of the literature was performed with the following guiding question: "Is trastuzumab more cost-effective than other anticancer agents in patients with metastatic breast cancer with over expression of HER2?"

Data sources

The following electronic databases were used to identify published studies on the cost-effectiveness of trastuzumab for metastatic breast cancer: MEDLINE (via PubMed), EMBASE (via Portal Saúde

Baseadaem Evidências), LILACS (via BIREME), Web of Science and Science Direct. Registers from the Cochrane Collaboration (via BIREME), the National Health System of the United Kingdom through the NHSEED database and other international technological evaluation agencies of the International Network of Agencies for Health Technology Assessment (INAHTA) were also analyzed. To retrieve additional studies, the search was expanded using the Google scholar search engine. As a complement, a manual search for references cited in the relevant publications obtained was performed in the mentioned databases. The search was limited to the period from 1998 to 2013, and there were no language restrictions in this step.

The search strategy was designed based on the following descriptors and their synonyms of each database: MeSH for MEDLINE (trastuzumab AND breast neoplasms AND cost-benefit analysis AND secondary), EmTree for EMBASE (trastuzumab AND "cost effectiveness analysis" AND "breast metastasis")and Decs for LILACS [(trastuzumabe OR trastuzumab OR herceptin) AND ("custo-efetividade" OR "cost-benefit analysis" OR "cost effectiveness" OR "análisis costo-beneficio" OR "análise custo-benefício") AND ("neoplasias da mama" OR "câncer de mama" OR "breast neoplasms" OR "neoplasias de la mama") AND (secundário OR metastático OR secondary OR metastatic OR secundario)]. For the remaining electronic databases, keywords relating to the disease ("metastatic breast cancer"), intervention ("trastuzumab") and type of economic analysis ("cost effectiveness") were used with the necessary adaptations for each bibliographic database.

Studies from each database were placed in Microsoft® Excel (version 2010) spreadsheets to eliminate duplicates and create a reference database.

Selection of studies

Studies from the bibliographic search were independently analyzed by two researchers (T. S. A. and T. F. G. S.) to manually eliminate duplicate studies. The authors, titles and journal names were compared, along with the volume, number and year of the publication. The remaining studies were examined based on their title and abstract. Original studies that mentioned the technology, health problem studied and the type of economic evaluation (trastuzumab, metastatic breast cancer and cost-effectiveness analysis) in Portuguese, Spanish and English were selected.

Comments, editorials, letters, case studies, review articles, conference posters, systematic reviews and meta-analyses were excluded, as were duplicate studies performed by the same research group addressing the same object of the initial study. Studies that did not include information on costs and outcomes of the intervention, that addressed the impact of the metastatic breast cancer management costs on the health budget or that addressed the costs of therapeutic interventions used to correct adverse reactions caused by trastuzumab were also excluded from the review.

Articles selected as potentially relevant continued to the next step, in which they were thoroughly evaluated based on a full reading of the text, and only those that m*et al.* l eligibility criteria, mentioned below, were included in the systematic review.

- Study objective: To evaluate the cost-effectiveness ratio of trastuzumab or use it as a comparator.
- Population: Patients with metastatic breast cancer over expressing HER2, regardless of age.
- Intervention: Trastuzumab, both as monotherapy, to treat patients who received one or more chemotherapy treatments for metastatic breast cancer, or in combination with taxanes (paclitaxel or docetaxel), to treat patients who did not receive chemotherapy for their metastatic diseases.
- Control or comparison: Other anticancer drugs or no drugs.
- Outcomes: Overall survival, quality-adjusted life years (QALY), life years gained, mortality, time to progression and progression-free survival.

Disagreements in both steps regarding the inclusion or exclusion of studies in the review were resolved by a third reviewer (G. B. G. M.).

Data extraction and quality assessment of studies

The selected articles were fully read by the two reviewers, and the items listed below were independently extracted to a spreadsheet:

- Characteristics of the studies: identification of the article (title, author, journal, volume, number, year and country of publication), intervention and comparators used;
- Clinical characteristics of the treatments: line of therapy of the metastatic disease, previous use of trastuzumab, performance of a diagnostic test for the HER receptor, dosage;
- Characteristics of cost-effectiveness analyses: efficacy data sources, economic model, time horizon, perspective adopted, discount rate, drug costs, other costs, currency, outcomes evaluated, incremental cost-effectiveness ratio (ICER) and the author's conclusion.

Differences in the extraction of information were resolved by consensus with a third reviewer upon the reassessment of the original article.

The quality assessment was independently performed by two reviewers adopting the format used by Teerawattananon *et al.* [10] with two different approaches. First, the practices reported for economic evaluation studies were assessed, namely, (a) the expression of the perspective used; (b) the description of the interventions to be compared; (c) the relationship between time horizon and discount; (d) the ICER data; (e) sensitivity analysis; and (f) the financial support statement.

The studies were assessed in a second stage according to the quality of the evidence used [11, 12]. The items comprising this assessment were: (a) the size of the clinical effects; (b) adverse events and complications; (c) basal clinical data; (d) the use of resources; (e) costs; and (f) utility (only applicable to cost-utility analyses). Coyle & Lee [11] asserted that it is necessary to identify specific factors related to the data sources for the main parameters that determine their suitability regarding the economic analysis in question. The data sources of each component were ranked from 1 to 6 in descending order. Studies are class 1 if the parameters are derived from the most reliable data sources. This quality assessment was summed using a table, in which the results found in each study were organized.

Synthesis and analysis of results

Data were extracted and interpreted regarding the ICER of trastuzumab (combined or alone) in metastatic breast cancer. The costs were converted to Brazilian Real using the conversion tool available on the website of the Central Bank of Brazil (Banco Central do Brasil) [13], and the results were compared with the budget ceiling recommended by the World Health Organization (WHO), but in Brazilian currency. According to the WHO, developing countries should adopt the threshold of up to three times the value of their gross domestic product (GDP) per capita in cost-effectiveness analyses of new technologies [14, 15]. Information on the GDP and Brazilian population was obtained from the website of the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística) [16].

The selected studies presented the use of trastuzumab in two different ways: as a first-or second-line therapy for metastatic breast cancer. The use of trastuzumab was performed alone or combined with other drugs. Given these characteristics, the conclusions of the cost-effectiveness analyses regarding the introduction of trastuzumab were grouped according to the existence of previous treatment of the metastatic diseases of patients.

RESULTS

Search and selection of studies

In total, 521 studies were identified. Of these, 161 were excluded due to being duplicates, leaving 360 studies. A total of 294 studies were discarded after reading their titles because they did not meet the criteria specified for this step (studies related to the cost-

effectiveness analysis of trastuzumab in metastatic breast cancer). Studies on the use of trastuzumab as an adjuvant and neoadjuvant therapy for breast cancer were excluded. Studies whose titles were not clear regarding the inclusion criteria were added to the subsequent step of reading of the abstracts, along with the other studies identified. A total of 66 studies were selected for reading of their abstracts. Forty-two studies were excluded by the same criteria mentioned previously, resulting in 24 studies to be fully read. No studies were excluded for being in a different language from those established for the present review. No additional studies were included by searching gray literature or by manually searching the references cited in the relevant publications obtained.

In the second step of the selection, 11 studies were excluded because 10 were conference posters, and 01 was an abstract of a technology evaluation report, whose objective was not to evaluate trastuzumab but to evaluate another drug. Finally, 13 studies comprised the present systematic review.

Data extraction and quality assessment of studies

Regarding the publication countries, 12 studies involved countries from North America and Europe. Only one study was developed in Brazil.

The studies were conducted within the last 10 years. The therapeutic regimens adopted in the cost-effectiveness analyses differed: eight studies compared the treatment with trastuzumab as a first-line therapy for metastatic disease, and five studies compared it as a second-line therapy; three of these latter studies used trastuzumab as a comparator in the evaluation of the cost-effectiveness ratio of other therapies, not as an intervention.

Table 1 shows the main characteristics of the studies. Table 2 shows the characteristics related to the cost-effectiveness analyses. All the studies were grouped according to the use of trastuzumab as a first- and second-line treatment.

Table 1: Main characteristics of the studies included

Authors	Year	Country	Intervention	Comparator	HER2 test
Trastuzumab as 1st line therapy for metastatic disease					
[17]	2012	Greece	trast+dxt	docetaxel	not reported
[18]	2004	USA	IHC test, trast+txt for+3 IHC test confirmed by FISH for IHC+2 and+3, trast+txt IHC test confirmed by FISH for IHC+2, trast+txt IHC test, trast+txt for+2 and+3 FISH test, trast+txt for positive results trast+txt	paclitaxel	IHC IHC confirmed by FISH for IHC+2 and+3 IHC confirmed by FISH for IHC+2 IHC FISH none
[19]	2011	United Kingdom	trast+anastrozole	anastrozole	not reported
[20]	2009	USA	trast+chemotherapy	chemotherapy	IHC and/or FISH (without details)
[21]	2008	Sweden	IHC test, trast+dxt for+3 IHC test, trast+dxt for+2 and+3 IHC test confirmed by FISH for IHC+2 and+3, trast+dxt for FISH-positive results FISH test, trast+dxt for FISH-positive results	docetaxel	IHC IHC IHC confirmed by FISH for IHC+2 and+3 FISH
[22]	2005	Norway	trastuzumab+docetaxel trastuzumab+anthracycline+cyclophosphamide trastuzumab+paclitaxel	docetaxel anthracycline+cyclophosphamide paclitaxel	IHC
[23]	2009	France	trastuzumab (with or without taxanes)	Standard chemotherapy (taxanes and/or anthracycline-based chemotherapy)	IHC+3 and/or FISH
[24]	2008	France	trastuzumab+paclitaxel	conventional chemotherapy	IHC+3
Trastuzumab as 2nd line therapy for metastatic disease					
[25]	2005	Italy	Cyclophosphamide+low-dose methotrexate	Trastuzumab+paclitaxel	not reported
[26]	2012	United Kingdom	Lapatinib+capecitabine	Trastuzumab+capecitabine	not reported
[27]	2012	Brazil	Lapatinib+capecitabine	Trastuzumab+capecitabine	not reported
[28]	2010	Sweden	Trastuzumab+capecitabine	Capecitabine	IHC or FISH
[29]	2005	Belgium	Trastuzumab	no trastuzumab (details not reported)	FISH

Legend: dxt: docetaxel; USA: United States of America; FISH: fluorescence in situ hybridization; IHC: immunohistochemical; trast: trastuzumab; txt: paclitaxel.

Table 2: Main characteristics related to cost-effectiveness analyses

Authors	Economic model	Time horizon	Perspective	Discount rate	Currency, year	Costs of drugs	Other costs	Outcomes evaluated
Trastuzumab as 1st line therapy for metastatic disease								
[17]	Area under the curve	12 years	Third-party payer	3.5%	Euro, 2011	Trastuzumab: €3280/g Docetaxel: €5950/g	Infusion, consultations and other drugs	Life years, QALY
[18]	Markov	Lifetime	Society	3%	American dollar,	Trastuzumab: US$ 2301/cycle	Diagnostic tests, outpatient infusion,	Life years, QALY

					2002	(no waste) Paclitaxel: US$ 1848/cycle	medical visit, pre-CT drugs, adverse reactions (treatment and monitoring), tickets, post-treatment progression and productivity of patients	
[19]	Markov	20 years	National Health System of the United Kingdom	3.5%	Pound sterling, 2008-2009	Trastuzumab: £1657.86/loading dose and £1292.88/regular dose Anastrozole: £68.56/box with 28 tablets	Pharmaceutical services, heart rate monitoring, outpatient care, supportive care pre and post-progression, exemestane, drug waste, terminal treatment	Life years, QALY
[20]	Markov	18 years	Not reported	3%	American dollar, 1998	Not reported	Costs of the diagnostic test, monitoring and treatment of adverse reactions	QALY
[21]	Markov	Lifetime	Society	Not reported	Swedish Krona (SEK), 2005	Docetaxel: SEK 15406/cycle Trastuzumab: SEK 5653/week	Diagnostic tests, outpatient care, adverse reactions (monitoring and treatment), palliative care, outpatient support after 1st line therapy	QALY
[22]	Comparison	40 weeks	Third-party payer	5%	Euro, 2003	Trastuzumab: €39454/patient treated Other drugs: not reported	Preparation and administration of chemotherapy, diagnostic test, daily outpatient rate, treatment and monitoring of adverse reactions	Life years
[23]	Design before and after	56 months	Hospital	Not reported	Euro, 2002	Not reported	Hospitalization, chemotherapy drugs and adjuvants, imaging and laboratory tests	Life years
[24]	Clinical trial	Cost: 24 weeks; Effectiveness: 14 months	Hospital	Not reported	Euro, 2002	Trastuzumab: €4200/g Paclitaxel: €4600/g Docetaxel: €8000/g Epirubicin: €1900/g	Diagnostic tests, pre-treatment assessment, monitoring, daily hospital rate	Life years
Trastuzumab as 2nd line therapy for metastatic disease								
[25]	Comparison of clinical trials	Not reported	National Italian health system	Not reported	Euro, 2003	CTX+MTX: €38/patient Trast+paclitaxel: €42423/patient	Administration of chemotherapy, hospitalization, medical visits, clinical tests, supportive care, administration of support treatment	Progression-free life years and overall tumor response
[26]	Area under the curve	5 years	National health system of the United Kingdom	3.5%	Pound, 2008	lap+cap: £13835/patient trast+cap: £12780/patient	Preparation, administration, medical visits, hospitalization, laboratory and imaging tests, radiotherapy	Life years, progression-free and post-progression life years, QALY
[27]	Area under the curve	5 years	National Brazilian health system	5%	Brazilian Real, 2010	lap+cap: R$66775/patient trast+cap: R$88833/patient	Medical care, hospital care, laboratory and imaging tests	Years, progression-free survival years, QALY
[28]	Markov	Lifetime	Swiss health	0%	Euro,	Capecitabine:	Preparation and	QALY

			system		2009	€1.29/tablet at0,15 g and €3.85/tablet at0,5 g Trastuzumab: €5250/g	administration of chemotherapy, laboratory tests, treatment and monitoring of adverse reactions, disease progression treatment	
[29]	Developed by the authors	Lifetime	Hospital or care provider	Not reported	Euro, 2002-2003	Not separately reported from the total cost of the disease	Professionals involved, drugs, materials, equipment, hospitalization, preparation of drugs, sterilization of materials, equipment maintenance, laboratory tests, surgical procedures	Life months

Legend: cap: capecitabine; tab: tablet; CTX: cyclophosphamide; lap: lapatinib; MTX: methotrexate; QALY: quality-adjusted life years; CT: chemotherapy; trast: Trastuzumab.

Regarding effectiveness, most economic evaluations based their efficacy estimates on the results from four controlled randomized clinical trials: three economic evaluations based on Marty *et al.* [30], three based on Slamon *et al.* [31], three based on Von Minckwitz *et al.* [32] and one evaluation based on Kaufman *et al.* [33]. Four economic evaluations used results from non-randomized studies, including one comparison of the mean survival between two single-arm clinical studies [25], one phase II clinical trial [29], one before-and-after design study of a single treatment center [23] and one comparison of the results between four treatment centers that treated patients with trastuzumabe, with six centers that did not treat patients with trastuzumab [24]. Similar to the effectiveness, comparators and treatment regimens were also selected based on randomized controlled clinical trials. The trastuzumab dose was very similar among the studies, ranging from a loading dose of 0.004 g/kg, followed by 0.002 g/kg weekly, to 0.008 g/kg as the loading dose and 0.006 g/kg every 3 weeks. There was a wide variety of other drugs used as comparators that were already used in the treatment of the metastatic disease (anastrozole, anthracyclines, capecitabine, cyclophosphamide, lapatinib, methotrexate, docetaxel, and paclitaxel) [34]. Most studies reported using one or two biochemical tests to determine the HER2 status in the tumor cell membrane. However, only Elkin *et al.* [18] and Lidgren *et al.* [21] listed the cost-effectiveness results for each HER2 test strategy used.

The Markov model was the most used economic method among the evaluations. Two (progression-free and post-progression) to three (stable disease, response, progressive disease) stages were used, followed by death. There was great variation between the time horizons adopted by the studies, from 24 weeks to the lifetime of the patient.

Most of the evaluations used direct costs, from the perspective of the national health system, whereas two evaluations used the society's perspective. The resources used varied drastically between these evaluations. For example, one of them used only medical visits and the administration of drugs [17], whereas another evaluation also used palliative care [19]. In addition, five evaluations did not report the use of the discount rate in the costs or outcomes [21, 23-25, 29], and there was even one evaluation [28] that reported that their costs and outcomes were not discounted (0%).

Similar to the effectiveness data, all economic evaluations also obtained the values of outcomes from studies published in the literature.

All the studies calculated the ICER, shown in table 3. Because two studies [25, 27] reported the ICER regarding two outcomes different from the remaining studies, this ratio was removed from the table, leaving only calculations related to life years and QALY gained.

Table 3: Results of the incremental cost-effectiveness ratio

Authors	Additional cost	Additional life years	Additional QALY	ICER (cost per life years)	ICER (cost per QALY)	Conclusion of the authors
Trastuzumab as 1st line therapy for metastatic disease						
[17]	€27323.98	0.729	0.449	37759.97	€61323.33	Cost-effective
[18] IHC confirmed by FISH for IHC+2 and+3, trast+txt vs no test, txt	US$10388	Not applicable	0.08	Not applicable	US$125100	Cost-effective
[18] FISH, trast+txt for positives vs IHC confirmed by FISH for IHC+2 and+3, trast+txt	US$1036	Not applicable	0.01	Not applicable	US$145400	Cost-effective
[19]	£37899	0.669	0.545	Not reported	£69514	Not cost-effective
[20]	US$47728	Not applicable	0.56	Not applicable	US$85676	Not reported
[21] IHC confirmed by FISH for IHC+2 and+3, trast+dxt vs no test, dxt	SEK85064	Not reported	0.176	SEK332252	SEK485039	Cost-effective

[21] FISH, trast+dxt vs IHC confirmed by FISH for IHC+2 and+3, trast+dxt	SEK8442	Not reported	0.015	SEK384427	SEK561207	Cost-effective
[22]	€44196	0.3 to 0.7	Not applicable	€69212 to €162417	Not applicable	Not cost-effective
[23]	€26812	1.5	Not applicable	€17874.66	Not applicable	Cost-effective
[24]	€21980	1.43	Not applicable	€15370	Not applicable	Cost-effective
Trastuzumab as 2st line therapy for metastatic disease						
[25]	€64164	0.477 progression-free life years	Not applicable	€134516/progression-free life years	Not applicable	Not cost-effective
[26]	€107	0.019	0.031	Dominated	Dominated	Not cost-effective
[27]	R$18430	0.23	0.131	Dominated	Dominated	Not cost-effective
[28]	€33980	Not applicable	0.35	Not applicable	€98329	Not cost-effective
[29]	€3258.42	0.82 life months	Not applicable	€3981.44/life months gained	Not applicable	High cost-effectiveness ratio

Legend: dxt: docetaxel; FISH: fluorescence in situ hybridization; ICER: incremental cost-effectiveness ratio; IHC: immunohistochemical; QALY: quality-adjusted life years; trast: trastuzumabe; txt: paclitaxel.

Of the eight evaluations that used trastuzumab as a first-line therapy, five concluded that this drug could be considered cost-effective. Of these, three evaluations [17, 21, 23] specified the threshold against which the ICER was compared. One evaluation related a minimum value that the society was willing to pay (*"willingness to pay")* for health improvements [18], and another reported that the ICER was "considered as acceptable in a developed country where the health system is willing to offer the population full access to innovative treatments." [24]. All the studies that used trastuzumab as a second-line therapy did not consider the intervention as cost-effective.

Regarding the first approach of the quality assessment (table 4), and following the methodology for economic evaluations [10], the least met criteria were the use of the discount rate (53.8%) and disclosure of funding sources (61.5%).

The ICER was calculated in all the studies. Two studies [24, 29] did not perform the sensitivity analysis, whereas four did not report the perspective used in the evaluations [19-24]. Four other studies [18, 20, 22, 29] did not adequately describe the comparators used (dosage and duration of treatment).

Table 4: Results of the first stage of the quality assessment

Recommendations	Number of studies fulfilling recommendation	Percentage (%)
Perspective specified	09	69.2
Descriptionof comparators	09	69.2
Used discounting for costs and/oroutcomes iftime horizonwas>1 year	07	53.8
Calculated and reported ICER	13	100
Performed uncertainty analysis	11	84.6
Disclosed funding sources	08	61.54

Table 5 shows the second approach adapted by Cooper *et al.* [12]. The utilities and base clinical data criteria were not mandatory for every article, and thus were the least met criteria. Eight studies used randomized controlled clinical trials, measuring end results, to insert clinical effects data into economic evaluations, except for five studies [20, 23-25, 29]. Only three studies collected their own administrative (hospital) data to define the types and amount of resources used during the treatment of metastatic breast cancer [23, 24, 29].

Table 5: Representation of results of the second stage of the quality assessment

Evidence rank	Size of clinical effects/adverse events and complications [n (%)]	Base clinical data (if applicable) [n (%)]	Use of resources [n (%)]	Costs [n (%)]	Utilities (if applicable) [n (%)]
1+					
1	8 (61.5)	3 (60)	3 (25)	12 (92.3)	
2+					
2			7 (58.3)	1 (7.7)	
3+					
3					8 (100)
4	4 (30.8)	2 (40)			
5					
6			2 (16.7)		
9	1 (7.7)				

Summary and analysis of results

The ICERs were converted to Brazilian Real (R$) to be compared with the threshold usually recommended by technology evaluation agencies and adopted by the Department of Science and Technology of the Ministry of Health (table 6). According to WHO, a technology is considered to be very cost-effective if the ICER is less than the GDP per capita, cost-effective if the ICER is between 1 and 3 times the GDP per capita, and not cost-effective if the ICER is greater than 3 times the GDP per capita [15].

Table 6: Results of the incremental cost-effectiveness ratio using costs transformed into Brazilian Real

Authors	Additional cost (R$)	Additional life years	Additional QALY	ICER (cost per life years) (R$)	ICER (cost per QALY) (R$)
Trastuzumab as 1st line therapy for metastatic disease					
[17]	87521.44	0.729	0.449	120056.84	194925.25
[18]	24170.80	Not applicable	0.08	Not applicable	302135.00
IHC confirmed by FISH for IHC+2 and+3, trast+txt vs no test, txt					
[18]	2410.56	Not applicable	0.01	Not applicable	241056.00
FISH, trast+txt for positives vs IHC confirmed by FISH for IHC+2 and+3, trast+txt					
[19]	144524.05	0.669	0.545	216029.97	265181.74
[20]	111053.51	Not applicable	0.56	Not applicable	198309.83
[21]	30342.33	Not reported	0.176	118514.28	172399.60
IHC confirmed by FISH for IHC+2 and+3, trast+dxt vs no test, dxt					
[21]	3011.26	Not reported	0.015	137125.11	200750.66
FISH, trast+dxt vs IHC confirmed by FISH for IHC+2 and+3, trast+dxt					
[22]	141564.21	0.3 to 0.7	Not applicable	202234.58 to 471880.70	Not applicable
[23]	85881.52	1.5	Not applicable	57254.35	Not applicable
[24]	70404.14	1.43	Not applicable	49233.66	Not applicable
Trastuzumab as 2st line therapy for metastatic disease					
[25]	205523.71	0.477 progression-free life years	Not applicable	430867.31/progression-free life years	Not applicable
[26]	342.73	0.019	0.031	Dominated	Dominated
[27]	18430	0.23	0.131	Dominated	Dominated
[28]	108841.34	Not applicable	0.35	Not applicable	310,975.25
[29]	10437.05	0.82 life months or 0.0683 life years	Not applicable	12728.11/life months gained or 152811.85/life years	Not applicable

Based on the R$ 67,206.00 Brazilian threshold (3 × GDP per capita of R$ 22402.00), none of the evaluations reported an ICER that allows trastuzumab to be considered cost-effective.

DISCUSSION

The present review indicated that the use of trastuzumab, alone or in combination, was cost-effective as a first-line therapy for metastatic disease, in contrast to when it is used as a second-line therapy. In the five studies that used trastuzumab as a second-line therapy, four authors [26-29] stated that the differences in the drug prices were the main responsible factors for the differences between the treatments. Bocci *et al.* [25] stated that their intervention (cyclophosphamide+methotrexate) represented a "good value for money and efficient use of health care resources".

Important limitations were observed in some economic evaluations, particularly in those that used non-randomized approaches to estimate efficacy data [23,24]. Comparing the results of different treatment centers, as performed by Poncet *et al.* [24], using the time ("before-and-after"), as Perez-Ellis *et al.* [23] did, or making indirect comparisons between different clinical trials, as performed by Bocci *et al.* [25], Delea *et al.* [26] and Machado & Einarson [27], may be biased if there are differences between the trials regarding the methods (for example, treatment and measurement of results) or characteristics of the patients that modify the effects of the compared treatments. There is a strong recommendation to use the highest evidence levels when assessing the efficacy of interventions. Randomized clinical trials, syntheses of systematic reviews and meta-analyses are the most robust studies because their design allows controlling for potential biases and confounding factors [9, 14, 35].

Currently, there are two biochemical assays on the market to determine the HER2 status in tumor cell membranes. The immunohistochemical (IHC) assay tests the overexpression of the HER2 protein, whereas the fluorescence in situ hybridization (FISH) detects the amplification of the HER2 gene. This latter test is considered as a gold standard, but it is also the most expensive one [36].

The studies of Elkin *et al.* [18] and Lidgren *et al.* [21] combined the use of the HER2 test with the treatment strategy, and this test had an important influence on the cost-effectiveness ratio of the therapy. When the "test+treatment" strategies were compared, the differences between the tests (with the same treatments) could already make the strategy cost-effective. These two authors found that the most cost-effective strategy is to test all patients using IHC, followed by confirmation of IHC2+and IHC3+with FISH, a strategy that is consonant with the systematic review conducted by Dendukuri *et al.* [36], and trastuzumab plus chemotherapy for FISH-positive results. And also testing all patients with FISH and treatment of positives, if the threshold values are higher than those commonly practiced.

Another important point raised in the studies analyzed that may have generated different conclusions was the value of the drugs and resources used in different countries. The prices and expenses may vary according to the type of health system and the study's perspective. Any decrease in the costs would result in a subsequent decrease in the cost-effectiveness ratio [37]. Matter-Walstra *et al.*

[28], in their sensitivity analysis, showed that, depending on the body surface, a decrease of 30-60% in the cost of trastuzumab would result in an ICER below the threshold used in the study, indicating that the use of trastuzumab would be cost-effective as a second-line therapy.

Some evaluations excluded treatment beyond disease progression, whereas others considered trastuzumab waste when calculating its cost, a situation that does not always occur in clinical practice. There were other differences regarding the use of resources, such as considering the monitoring and treatment of adverse reactions, palliative care, and pharmaceutical services. All these factors contributed to the calculation of the total cost of the treatment, thus influencing the cost-effectiveness ratio. For Parkinson *et al.* [6], the rate of adverse reactions and their monitoring and treatment, the extension of treatment beyond progression, the level of trastuzumab waste and the use of chemotherapy after disease progression most likely can only be precisely determined after the widespread use of the intervention, instead of using data from a controlled randomized clinical trial.

In the present review, it was also found that the studies analyzed used different thresholds and decision analyses when evaluating the ICER of trastuzumab. The choice of a cost-effectiveness threshold depends on who is making the decision, what is the purpose of the analysis, how much the society is willing to pay for health improvements, what are the resources available, and how the decision maker values health, money and risk [38]. This explains the different cost-effectiveness thresholds found in the present review because the evaluation of authors from each country (even within the same country) was based on each one of the previously described factors. The two evaluations [23,24] that reported higher estimates for life years gained (approximately 1.5 life years gained) provided the lowest ICER, and these estimates may have influenced the ICER. This result occurred because these two evaluations used results from non-randomized studies, in which selection or allocation (patients with a worse prognosis in the comparator arm, for example) biases may have occurred that would overestimate the efficacy of trastuzumab.

The findings of the present systematic review are consistent with those of other published reviews on the subject. A literature search showed five systematic reviews on the cost-effectiveness ratio of trastuzumab in metastatic breast cancer: Lewis *et al.* [39]; Ferrusi *et al.* [40]; Blank *et al.* [37]; Fleeman *et al.* [19]; and Parkinson *et al.* [6]. The review by Ferrusi *et al.* [40] covered breast cancer treatment as a whole-initial and metastatic-but the other four reviews evaluated only the metastatic phase of the disease. The study by Lewis *et al.* [39] included only two economic evaluations, extracted from the submission of Roche to the National Health System (NHS) to obtain the trastuzumab registration. The study by Fleeman *et al.* [19] did not include any economic evaluation in their review; therefore, the authors decided to make their own cost-effectiveness analysis. The systematic review by Blank *et al.* [37] covered not only trastuzumab but also other anticancer drugs and molecular targeted agents. However, the authors did not perform a quality assessment. Parkinson *et al.* [6] did not use a formal methodology to assess the quality of the studies and only discussed issues that could affect the quality of an economic evaluation based on the checklist of Drummond *et al.* [41].

Regarding the quality assessment of the economic evaluations, the methodology used by Lewis *et al.* [39] and Ferrusi *et al.* [40] in their systematic reviews was the one developed by Drummond *et al.* [41]. This methodology results in a thorough interpretation of economic evaluations because it covers all the important items for its development and is presented as open questions. To make this methodology more practical, Lewis *et al.* [39] adapted it to a checklist with closed questions that could be answered by binary categorical variables (yes/no).

In the present review, the methodology used by Teerawattananon *et al.* [10] was adopted. The advantage of this method is that it provides a more thorough analysis of the evidence that was used as a basis to develop the economic studies. It was concluded that the included studies were of good methodological quality, both in the first and in the second approach, because there was little heterogeneity among the criteria evaluated.

The limitation of the present study was that the second approach of the quality assessment was not conducted by a third reviewer, a strategy that was different from the other steps of the systematic review. In addition, conference abstracts were excluded for not meeting the eligibility criteria, but they could contain relevant information on the cost-effectiveness ratio of trastuzumab for metastatic breast cancer.

CONCLUSION

The present study aimed to address the cost-effectiveness ratio of interventions with trastuzumab in the treatment of metastatic breast cancer, investigating whether the existing literature would allow drawing any conclusions about this issue. Secondarily, the study also allowed exploration of the main drivers of the conflicting conclusions among the authors, leading to the thorough examination of the cost-effectiveness ratio of trastuzumab for metastatic breast cancer. This was possible because the included economic evaluations showed differences in the modeling of costs, outcomes, treatment patterns between the countries (such as the method for HER2 tests) and thresholds considered for a technology to be cost-effective.

After converting the values used in the studies to Brazilian Real (R$), trastuzumab would not be considered cost-effective in any assessment using the Brazilian threshold. However, the differences in the use of resources and funding between the various health care systems may limit the transferability of foreign results into the Brazilian context. To consider trastuzumab as cost-effective for metastatic breast cancer, some topics must be considered: first, the treatment protocol (combination with other drugs or patients with or without recurrence). Second, the decision must also consider the use of the HER2 test and which HER2 status (2+and/or 3+, confirmed or not by FISH) will receive treatment because this test affects the cost-effectiveness results.

New cost-effectiveness analyses of trastuzumab for metastatic breast cancer are required, preferably combined with future randomized clinical trials in which data on the cost and effectiveness are collected simultaneously with the comparison of groups, providing more accurate data and allowing the comparison of the adverse effects profile of both therapies. It is also important that these economic evaluations cover new drugs already available for metastatic breast cancer (e. g., lapatinib and pertuzumab) to generate information useful particularly for treatment beyond progression (second-line or subsequent treatment).

Finally, any decisions on the incorporation of trastuzumab for the treatment of metastatic breast cancer in Brazil should not be based only on economic studies. The decision of introducing a new public health intervention should consider multiple factors, including, in addition to the effectiveness of the intervention, its safety, the financial costs of initiating and maintaining the treatment, the monitoring of the clinical results of its use and the necessary infrastructure to successfully provide the intervention, as well as the political will and equity promotion factors.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Instituto nacional do câncer josé alencar gomes da silva. Prevention and Surveillance Coordination. [Estimate 2014:Incidence of Cancer in Brazil]. Rio de Janeiro: INCA; 2014. p. 124.
2. Roché H, Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. Ann Oncol 2011;22(5):1000-10.
3. Morrow PKH, Zambrana F, Esteva FJ. Advances in systemic therapy for HER2-positive metastatic breast cancer. Breast Cancer Res 2009;11(4):207.
4. Kanagathara N, Kavitha K. Evaluation of HER2/neu over expression in breast cancer. Int J Pharm Pharm Sci 2014;6(2):898-900.

5. Chandel P, Harikumar SL. Pharmaceutical monoclonal antibodies: production, guidelines to cell engineering and applications. Int J Pharm Pharm Sci 2013;5(2):13-20.
6. Parkinson B, Pearson S, Viney R. Economic evaluations of trastuzumab in HER2-positive metastatic breast cancer: a systematic review and critique. Eur J Health Economics 2014;15(1):93-112.
7. BRASIL. Ordinance no. 18 of July 25. [Makes public the decision to incorporate trastuzumab into the Unified Health System for the treatment of locally advanced breast cancer]. Brasília: Diário Oficial da União; 2012;144:57.
8. BRASIL. Ordinance no. 19 of July 25. [Makes public the decision to incorporate trastuzumab into the Unified Health System for the treatment of initial breast cancer]. Brasília: Diário Oficial da União; 2012;144:57.
9. BRASIL. Ministry of Health. Secretariat of Science, Technology and Strategic Inputs. [Methodological guidelines: development of systematic review and meta-analysis of randomized controlled trials]. Brasília: Ministry of Health Publisher; 2012. p. 92.
10. Teerawattananon Y, Russell S, Mugford M. A systematic review of economic evaluation literature in Thailand; are the data good enough to be used by policy-makers? Pharmacoeconomics 2007;25(6):467-79.
11. Coyle D, Lee KM. Evidence-based economic evaluations: how the use of different data sources can impact results. In: Donaldson C, Mugford M, Vale L. Evidence–based health economics; from effectiveness to efficiency in systematic review. London: BMJ Publishing Group; 2002. p. 55-66.
12. Cooper N, Coyle D, Abrams K, Mugford M, Sutton A. Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997. J Health Serv Res Policy 2005;10(4):245-50.
13. Banco Central do Brasil. Currency Conversion [Internet] Brasília: Banco Central do Brasil. Available from: http://www4.bcb.gov.br/pec/conversao/conversao.asp. [Accessed 18 Dec 2013].
14. BRASIL. Ministry of Health. Secretariat of Science, Technology and Strategic Inputs. [Methodological Guidelines: health technologies economic evaluation studies]. Brasília: Ministry of Health Publisher; 2009. p. 145.
15. World Health Organization. Choosing interventions that are cost effective (WHO-CHOICE): Cost-effectiveness thresholds [Internet]. Genebra: World Health Organization. Available from: http://www.who.int/choice/costs/CER_thresholds/en/. [Accessed 18 Dec 2013].
16. Instituto Brasileiro de Geografia e Estatística. Indicators [Internet]. Brasília: Ministério do Planejamento, Orçamento e Gestão. Available from: http://www.ibge.gov.br/home/. [Accessed 18 Dec 2013].
17. Athanasakis K, Kyriopoulos J. A cost-effectiveness analysis of trastuzumab plus docetaxel vs. docetaxel alone for the treatment of HER2-positive metastatic breast cancer in the Greek healthcare setting. Forum Clin Oncol 2012;3(4):28-34.
18. Elkin EB, Weinstein MC, Winer EP, Kuntz KM, Schnitt SJ, Weeks JC. HER-2 testing and trastuzumab therapy for metastatic breast cancer: A cost-effectiveness analysis. J Clin Oncol 2004;22(5):854-63.
19. Fleeman N, Bagust A, Boland A, Dickson R, Dundar Y, Moonan M, *et al.* Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. Health Technol Assessment 2011;15(42):1-100.
20. Garrison Jr LP, Veenstra DL. The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. Value Health 2009;12(8):1118-23.
21. Lidgren M, Wilking N, Jönsson B, Rehnberg C. Cost-effectiveness of HER2 testing and trastuzumab therapy for metastatic breast cancer. Acta Oncol 2008;47(6):1018-28.
22. Norum J, Risberg T, Olsen JA. A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a model-based cost-effectiveness analysis. Annu Oncol 2005;16(6):909-14.
23. Perez-Ellis C, Gonçalves A, Jacquemier J, Marty M, Girre V, Roché H, *et al.* Cost-effectiveness analysis of trastuzumab (herceptin) in HER2-overexpressed metastatic breast cancer. Am J Clin Oncol 2009;32(5):492-8.
24. Poncet B, Bachelot T, Colin C, Ganne C, Jaisson-Hot I, Orfeuvre, *et al.* Use of the monoclonal antibody anti-HER2 trastuzumab in the treatment of metastatic breast cancer: a cost-effectiveness analysis. Am J Clin Oncol 2008;31(4):363-8. Erratum in. Am J Clin Oncol 2009;32(1):98.
25. Bocci G, Tuccori M, Emmenegger U, Liguori V, Falcone A, Kerbel RS, *et al.* Cyclophosphamide-methotrexate 'metronomic' chemotherapy for the palliative treatment of metastatic breast cancer: a comparative pharmacoeconomic evaluation. Annu Oncol 2005;16(8):1243-52.
26. Delea TE, Tappenden P, Sofrygin O, Browning D, Amonkar MM, Karnon J, *et al.* Cost-effectiveness of lapatinib plus capecitabine in women with HER2+metastatic breast cancer who have received prior therapy with trastuzumab. Eur J Health Econ 2012;13(5):589-603.
27. Machado M, Einarson TR. Lapatinib in patients with metastatic breast cancer following initial treatment with trastuzumab: An economic analysis from the Brazilian public health care perspective. Breast Cancer 2012;4:173-82.
28. Matter-Walstra KW, Dedes KJ, Schwenkglenks M, Brauchli P, Szucs TD, Pestalozzi BC. Trastuzumab beyond progression: a cost-utility analysis. Annu Oncol 2010;21(11):2161-8.
29. Neyt MJ, Albrecht JA, Clarysse B, Cocquyt VF. Cost-effectiveness of Herceptin®: a standard cost model for breast-cancer treatment in a Belgian university hospital. Int J Technol Assess Health Care 2005;21(1):132-7.
30. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23(19):4267-74.
31. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783-92.
32. Von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, *et al.* Trastuzumab beyond progression in human epidermal growth factor receptor 2–positive advanced breast cancer: a German breast group 26/Breast International Group 03-05 Study. J Clin Oncol 2009;27(12):1999-2006.
33. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, *et al.* Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27(33):5529-37.
34. Tkaczuk KHR. Review of the contemporary cytotoxic and biologic combinations available for the treatment of metastatic breast cancer. Clin Ther 2009;31:2273-89.
35. BRASIL. Ministry of Health. Executive Secretariat. Area of Health Economics and Development. [Economic evaluation and Health: Challenges for the management of the Unified Health System]. Brasília: Ministry of Health Publisher; 2008. p. 104.
36. Dendukuri N, Khetani K, McIsaac M, Brophy J. Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis. CMAJ 2007;176(10):1429-34.
37. Blank PR, Dedes KJ, Szucs TD. Cost effectiveness of cytotoxic and targeted therapy for metastatic breast cancer: a critical and systematic review. Pharmacoeconomics 2010;28(8):629-47.
38. OWENS, Douglas K. Interpretation of cost-effectiveness analyses. J General Intern Med 1998;13(10):716-7.
39. Lewis R, Bagnall A, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al.* A rapid and systematic review of the clinical effectiveness

and cost-effectiveness of trastuzumabe for breast cancer. Heslington: NHS Centre for Reviews and Dissemination; 2001. p. 102.

40. Ferrusi IL, Marshall DA, Kulin NA, Leighl NB, Phillips KA. Looking back at 10 years of trastuzumab therapy: what is the role of HER2 testing? A systematic review of health economic analyses. Per Med 2009;6(2):193-215.
41. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 1997. p. 182.