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ErbB2+metastatic breast cancer treatment after progression on trastuzumab: a cost-effectiveness analysis for a developing country

Tratamientos para cáncer de seno metastásico ErbB2+ en progresión Post-Trastuzumab: Análisis de costo-efectividad para un país en vía de desarrollo

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ABSTRACT

Objective Breast cancer (BC) and metastatic breast cancer (MBC) are significant causes of deaths amongst women worldwide, including developing countries. The cost of treatment in the latter is even more of an issue than in higher income countries. ErbB2 overexpression is a marker of poor prognosis and the goal for targeted therapy. This study was aimed at evaluating the cost-effectiveness in Colombia of ErbB2+ MBC treatment after progression on trastuzumab.
Methods A decision analytic model was constructed for evaluating such treatment in a hypothetical cohort of ErbB2+MBC patients who progressed after a first scheme involving trastuzumab. The alternatives compared were lapatinib+capecitabine (L+C), and trastuzumab+a chemotherapy agent (capecitabine, vinorelbine or a taxane). Markov models were used for calculating progression-free time and the associated costs. Effectiveness estimators for such therapy were identified from primary studies; all direct medical costs based on national fees-guidelines were included. Sensitivity was analyzed and acceptability curves estimated. A 3 % discount rate and third-payer perspective were used within a 5-year horizon.
Results L+C dominated its comparators. Its cost-effectiveness ratio was COP $49,725,045 per progression-free year. The factors most influencing the results were the alternatives' hazard ratios and the cost of trastuzumab.
Conclusion Lapatinib was cost-effective compared to its alternatives for treating MBC after progression on trastuzumab using a Colombian decision analytic model.

Key Words: Cost-benefit analysis, breast neoplasm, receptor, epidermal growth factor, Colombia (*source: MeSH, NLM*).

RESUMEN

Objetivo El cáncer de seno (CS) y cáncer de seno metastásico (CSM) son importantes causas de muerte entre las mujeres a nivel mundial y en países en vía de desarrollo. En estos últimos los costos de los tratamientos son aún más preocupantes que en países de alto ingreso. La sobreexpresión de ErbB2 es marcador de pobre pronóstico y objetivo de terapias dirigidas. Se evaluó la costo-efectividad de los tratamientos de CSM ErbB2+ en progresión post-trastuzumab en Colombia.
Métodos Se desarrolló un modelo analístico de decisiones para evaluar los tratamientos en una cohorte hipotética de CSM ErbB2+ que progresaron después de un primer esquema con trastuzumab. Las alternativas comparadas fueron: lapatinib+capecitabina (L+C), y trastuzumab más un agente quimioterápico (capecitabina, vinorelbinao un taxano). Se usaron modelos de Markov para calcular el tiempo libre de progresión y los costos asociados. Estimaciones de efectividad fueron identificadas de estudios primarios. Se incluyeron todos los costos médicos directos basados en los manuales tarifarios nacionales. Se realizaron análisis de sensibilidad y curvas de aceptabilidad. Se descontaron costos y resultados a una tasa anual de 3 %, la perspectiva de análisis fue del tercer pagador y el horizonte de 5 años.
Resultados L+C domina a sus comparadores con un razón de costo-efectividad de COP $49 725 045 por año libre de progresión. Los factores que más influencian los resultados son los hazard ratios de las alternativas y el costo de trastuzumab.
Conclusión Lapatinib es costo-efectivo comparado con sus alternativas para el tratamiento del CSM después de la progresión con trastuzumab en el escenario colombiano.

Palabras Clave: Análisis de costo-beneficio, cáncer de seno, receptores del factor de crecimiento epidérmico, Colombia (*fuente: DeCS, BIREME*).

Around 45 % of the more than 1 million breast cancer (BC) diagnoses and 55 % of BC-related deaths every year occur in developing countries (1). The 5-year recurrence-free mean survival rate worldwide is 60 % (2). Almost 50 % of BC patients develop metastatic disease (3). Retrospective analysis shows a decrease in metastatic breast cancer (MBC) incidence (4) and longer survival due to the introduction of new agents and targeted therapy (5); however, such tendency may be hindered in developing countries due to their lower income and other urgent health-related problems, such as infectious diseases.

MBC treatment is not seen as being curative but mainly palliative, concentrating on an improvement in the progression-free survival and patients' quality of life (6).

Due to the development of inactivating-only targeted drugs, epidermal

growth factor receptors (EGFR) and hormone receptors represent significant biological markers in BC and MBC treatment. EGFRs (ErbB1 and ErbB2) have been found to be overexpressed in around 25 % of primary BC (7-10); it is associated with poor prognosis (lower recurrence-free (RF) and overall survival (OS) rates) (7-12).

Trastuzumab alone or combined with first-line chemotherapy in phase III clinical trials has given better overall response (OR), time to progression (TP) and OS rates than chemotherapy alone in ErbB2+MBC patients (13-16). Evidence of trastuzumab use in Erb B2+MBC which has progressed after trastuzumab-based therapy mainly consisted of retrospective analysis and limited-sized phase II studies (17-30). One phase III study (31-32) found that trastuzumab + capecitabine had better OR, clinical benefit (CB) and TP rates than capecitabine alone.

Lapatinib is an oral, small molecule which selectively and reversibly inhibits the tyrosine-kinase signalling pathways for ErbB2+ErbB1 and EGFR which are useful in MBC cases where resistance to trastuzumab has developed (18, 29). L+C has been shown to be superior to capecitabine alone in patients who have previously been treated with trastuzumab (33-34). This study was aimed at assessing the cost-effectiveness of L+C compared to trastuzumab plus chemotherapy for ErbB2+MBC in Colombia.

MATERIALS AND METHODS

The alternatives assessed here were (L+C) compared to trastuzumab + capecitabine (T+C), trastuzumab + paclitaxel (T+P), trastuzumab + docetaxel (T+D), and trastuzumab + vinorelbine (T+V). Trastuzumab-based strategies represent current practice in Colombia, although the different alternatives coexist.

A three-state Markov model for the natural history of MBC was constructed (Figure 1). The model simulated a cohort of MBC women whose cancer had already progressed after a trastuzumab first scheme. Initial state was called progression free survival (PFS). Patients were treated with L+C or trastuzumab plus chemotherapy, according to the alternative, until they progressed again (and moved on to the progression (P) state). Only palliative care was administered from then on.

Indirect comparisons were made in the absence of head-to-head studies.

The sources of evidence for estimating probability were the ErbB2+ subgroups of clinical trials comparing T+C to capecitabine (32) and L+C to capecitabine (33). Disease-free survival (DFS) and OS rates were estimated as Weibull functions for each chemotherapy alone from the survival curves reported in the literature and multiplied by the hazard ratios (HR) from trastuzumab and lapatinib studies.

Figure 1. Markov model, natural history of MBC

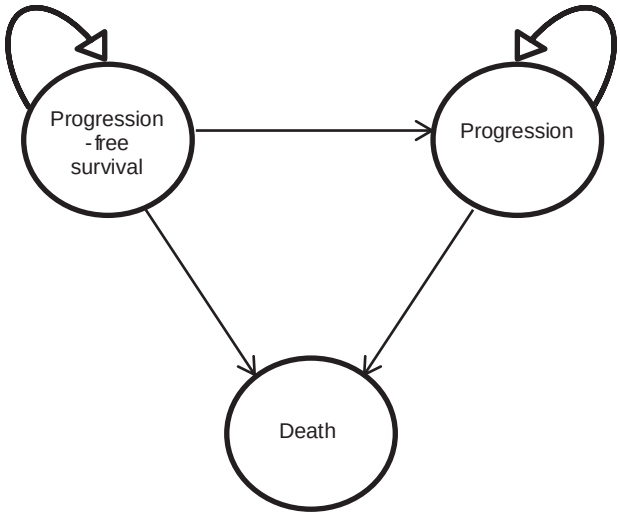


Table 1. Parameters for the model

Estimation	Average	Standard Error	Distribution	Source
Weibull parameters survival functions DFS				
Capecitabine monotherapy				
Lambda	0.0053		Bootstrap	Geyer (33)
Gamma	1.25		Bootstrap	
HR Lapatinibpluscapecitabinevs. Capecitabinemonotherapy	0.59	0.125	Lognormal	
HR Trastuzumabpluscapecitabinevs. Capecitabine monotherapy	0.685	0.1244	Lognormal	Von Minckwitz G (32)
OS				
Lapatinibpluscapecitabine				
Lambda	0.0019		Bootstrap	Geyer (33)
Gamma	1.61		Bootstrap	
HR Lapatinib + capecitabinevs capecitabinemonotherapy	0.92	0.27	Lognormal	
HR Trastuzumabpluscapecitabinevs. capecitabinemonotherapy	0.763	0.1882	Lognormal	Von Minckwitz G (32)

PSA: probabilistic sensitivity analysis

The models supposed all types of chemotherapy to be equally effective, only differing regarding their cost and adverse events. Table 1 gives the

parameters used in the model and their sources.

ErbB2+metastatic breast cancer care protocols and adverse events in a Colombian setting were validated by peer consensus. Direct care costs were identified for each event based on the Colombian Social Protection Ministry's SISPRO database drug cost information system and national fees guidelines (SOAT 2009) (Table 2).

Progression-free time was the outcome and discount rate 3 %. The perspective adopted was that of the third payer, including all direct medical costs. The time horizon was 5 years. Incremental cost-effectiveness ratios were calculated. Deterministic and probabilistic sensitivity analysis included acceptability curves for each alternative.

Table 2. Data used in the model

Generic name	Pharmaceutical form	Strength	Cost 2009	Dose
Trastuzumab	Infusion lyophilized powder container by vial	440 mg	COP $6,926,888.00	2mg/Kg IV weekly until progression evidence
Lapatinib Ditosylate Monohydrate	Coated tablet container by 70 tablets	250 mg	COP $47,630.14	1250 mg daily
Capecitabine	Tablet (folding container by 8 tablets)	500 mg	COP $18,484.11	14 days cycles 2000 mg/ m^2SC daily with washout for 7 days
Vinorelbine	Vial 50 mg/ 50 mL	50 mg	COP $363,050.80	25mg/m^2SC weekly for two weeks, washout the third week and then restarting
Paclitaxel	Vial 100 mg/ 16.7 mL	100 mg	COP $169,718.84	175 mg/m^2SC once every three weeks for six cycles
Docetaxel	Vial 20 mg / 0.5 mL (Container with one ampoule)	20 mg	COP $97,155.87	35 mg/m^2SC weekly for three weeks, with washout the fourth week and then restarting

RESULTS

L+C was the most effective and least expensive alternative (i.e. dominant) (Table 3). L+C cost-effectiveness ratio was COP $49,725,045 per progression-free year (average Colombian exchange rate in 2009 was COP $2,156 per dollar).

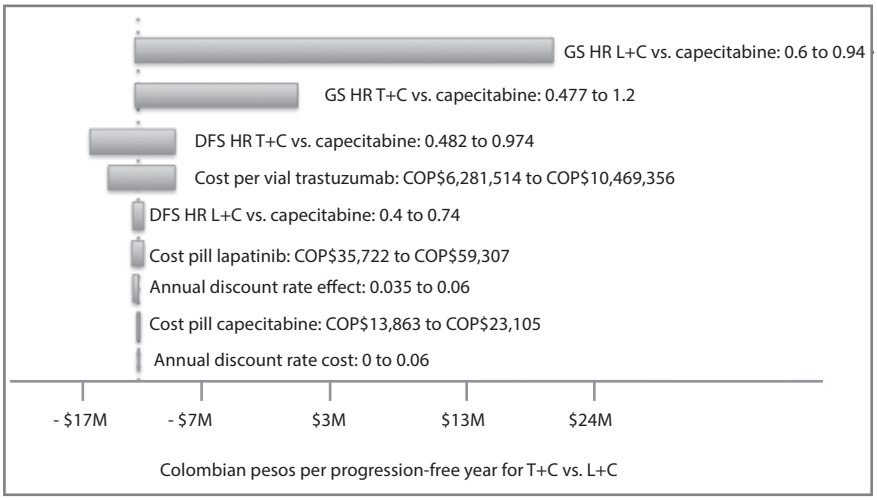
Four variables accounted for 99.4 % of variability in the results: T+C *cf* capecitabine OS and DFS HR, L+C *cf* capecitabine OS and the cost per vial of trastuzumab (Figure 2). Tornado analysis results for the other alternatives were very similar (data not shown).

A probabilistic sensitivity analysis with 10,000 simulations (Figure 3) showed that L+C was dominant for 50.13 % of the simulations and was still cost-effective in the remaining 49.87 % cases, as the ICER for the alternatives exceeded the three times per-capita GDP threshold (three times COP $11,216,656). Similar results were produced when trastuzumab was accompanied by taxane or vinorelbine (data not shown).

Table 3. Cost-effectiveness analysis

Strategy	Cost	Incremental Cost	Effectiveness	Incremental effectiveness	CE	ICER
L+C	COP $82,017,207		1.649		COP $49,725,045	
T+C	COP $111,679,005	COP $29,661,798	1.631	-0.018	COP $68,442,394	Dominated
T+P	COP $100,284,893	COP $ 18,267,686	1.631	-0.018	COP $61,459,521	Dominated
T+D	COP $ 104,594,593	COP $22,577,386	1.631	-0.018	COP $64,130,406	Dominated
T+ V	COP $ 105,313,611	COP $23,296,404	1.631	-0.018	COP $ 64,541,367	Dominated

Figure 2. Tornado diagram at T+C vs. L+C.



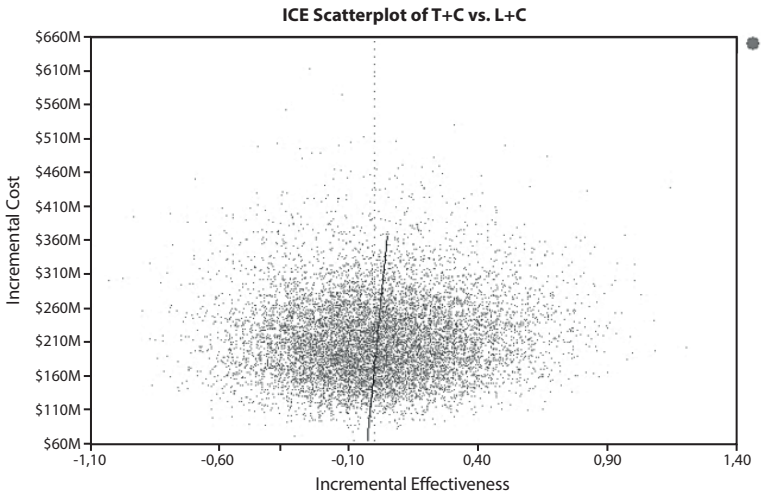
DISCUSSION

This cost-effectiveness analysis showed that the lapatinib-based strategy was dominant in MBC treatment after ErbB2+ progression on trastuzumab compared to trastuzumab with capecitabine, taxane or vinorelbine.

A benefit not included in this analysis was that the lapatinib strategy only

required oral administration, implying a positive impact on patients' quality of life. A cost-utility analysis was not made as there are no evaluations of states of health have been made in Colombia; instead, the result was expressed in DFP years because OS was not significantly different in the alternatives.

Figure 3. Probabilistic sensitivity analysis



ICE: incremental cost effectiveness

Our analysis did not include other strategies as comparators because they are not accepted in Colombia as oncological treatment. The results were subject to commercial and regulatory practice determining the prices and packing-sizes used in Colombia.

Although there was no cost-effectiveness threshold for Colombia, we used WHO recommendations in terms of annual per capita GDP; however, as lapatinib dominated the alternatives currently being used in Colombian medical practice, the result was robust regarding the threshold.

This study's limitations included treatment-effectiveness data being obtained from international studies which obviously used different populations to the Colombian population. If treatment effectiveness and complication frequency were significantly different from that considered in this study, the results would also have been different. Given a lack of head-to-head studies comparing the alternatives being studied, the comparisons

in this analysis were indirect and based on HRs from existing randomized clinical trials; the results would thus vary for direct comparison. Due to data being unavailable for determining chemotherapy effectiveness, a strong assumption was required in taking the same effectiveness, implying that therapy would differ only regarding cost and adverse events.

Prior economic analysis has dealt with trastuzumab in ErbB2+MBC progression (35-46) but only two have compared it to L+C (47, 48). One found that L+C ICER exceeded the threshold per QALY gained for the USA; the other found that L+C was dominant for the UK, as it provided greater QALY at lower cost compared to T+C or T+V or trastuzumab only. Another analysis comparing L+C *cf* T+C for Mexico (49) was based on results from an interrupted clinical trial (50). So far no full-length article has been published for a developing country. This is the first complete cost-effectiveness analysis comparing two human epidermal growth receptor inhibitors in advanced MBC for a developing country.

Current trastuzumab-based practice relies on using the same treatment, even after patients have developed resistance to it. Developing countries must have access to cost-effective alternatives thereby enabling ErbB2+metastatic breast cancer to be faced while keeping the fiscal burden at bay •

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Authors' contributions: LC, MG and OG were responsible for the concept and design, OG and CC for data collection and assembly, LC, MG and OG for data analysis and interpretation, LC, MG, OG and CC for writing the manuscript and LC, MG, OG and CC for final approval.

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