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Review Article

Cost Effectiveness of Trastuzumab in Metastatic Breast Cancer in South Africa: A Systemic Review

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Summary

This paper gave an overview on MBC in Chapter 1. It further outlined treatment options in metastatic breast cancer with specific view of cost effectiveness of trastuzumab in MBC. Research questions were generated and objectives of this review paper were listed.

In Chapter 2, various health economic evaluations were discussed namely, CEA, CUA and CBA. However, CEA was selected for this paper based on its approach to give outcomes in ICER per QALY of a drug intervention, trastuzumab in MBC. Furthermore, methodology on literature review on studies conducted using PubMed, Cochrane and Google search on scholarly articles. The choice of the final articles was based on an outlined inclusion and exclusion criteria. The results of these selected studies were reported.

In the last Chapter, discussion of the results was discussed in context to the South African situation to try answer the research questions generated in Chapter 1. Based on the CEA results and the assumed WHO WTP threshold, trastuzumab use in MBC is considered not cost effective with an estimated WTP in SA.

Finally, recommendations were made to consider trastuzumab cost effective from a public sector perspective.

List of Abbreviations

ASCO: American Society of Clinical Oncology.

BRICS: Brazil, Russia, India, China and South Africa.

CBA: Cost benefits analysis.

CEA: Cost effectiveness analysis.

CUA: Cost utility analysis.

ESMO: European Society of Medical Oncology.

FDA: Food and Drug Administration.

FISH: Fluorescence in Situ Hybridization.

GDP: Gross domestic product.

HER2: human endothelial receptor 2.

ICER: Incremental cost effectiveness ratio.

IHC: Immunohistochemistry.

MBC: Metastatic breast cancer.

MCBS: Magnitude of Clinical Benefit Scale.

MESH: Medical subject heading.

NICE: National Institute for Health and Care Excellence.

OS: Overall survival.

PFS: Progression free survival.

QALY: Quality adjusted life years.

SA: South Africa.

SAMHS: South African Military Health Services.

SEER: Surveillance, Epidemiology, and End Results.

UK: United Kingdom.

USA: United States of America.

USD: United States dollars.

WHO: World Health Organization.

WTP: Willingness to pay.

ZAR: South African rand.

Introduction

Background

In the last decade the term ‘cancer survivor’ has become quite popular as more and more patients are living their lives longer and longer with an oncological diagnosis. A prime example for these medical advances is breast cancer patients. Currently large population based databases show a 5-year survival of about 93% over all stages (SEER). Even though this is very promising, Narod, et al. (2015) reported that the survival still depends very much on the stage it is diagnosed (Figure 1.1). Moreover, Blank, et al. (2010) estimated that 25-40% of breast cancer patients present or will develop metastasis in the history of their disease.

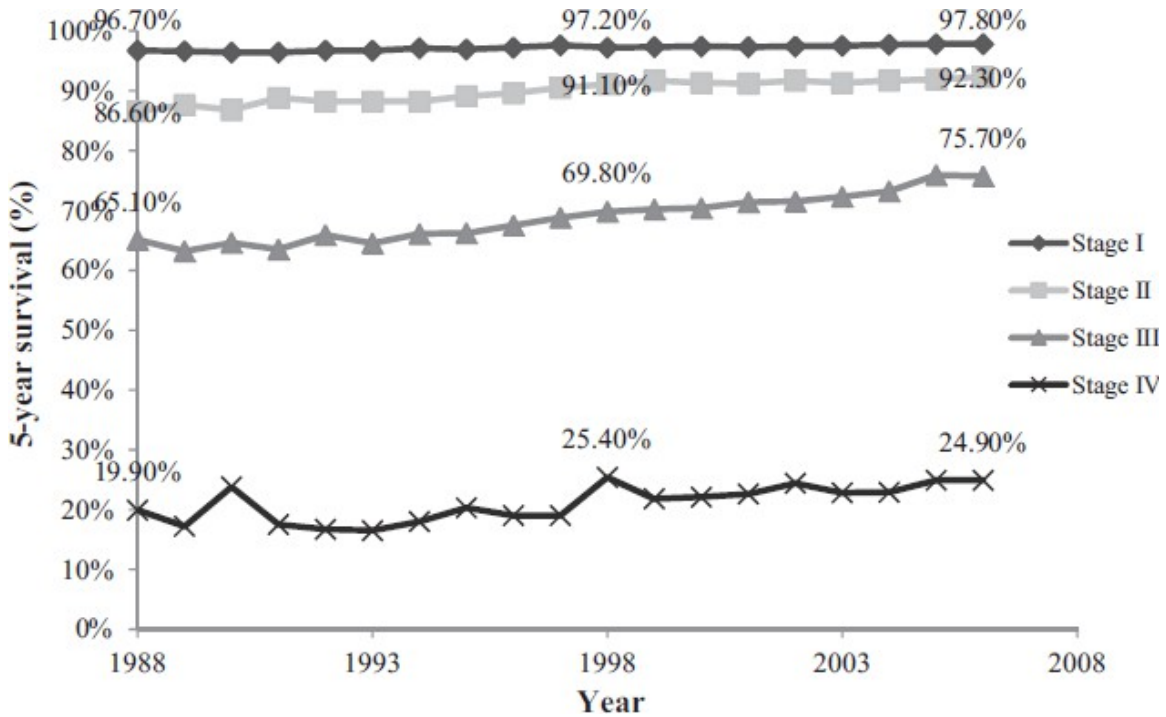

Figure 1.1: Breast cancer stage presentation and survival outcomes

Source: Narod et al. 2015

Cardoso, et al. (2017) also argued that the survival trends improved a lot where the median overall survival improved from 14 months in 1991 to 21 months in 2001 in a decade. Therefore, it is imperative that clinicians become knowledgeable in treatment options of metastatic breast cancer. Furthermore, Smieliauskas, et al. (2014) reported that even though there are various options (Table 1.1) in treatment of metastatic breast cancer, the disease is not curable. Therefore, the goals of treatment are palliative care:

- To prolong life.
- To reduce and to control burden of disease.
- To minimize cancer related symptoms and complications.
- To maintain the quality of life.

Therapy	Role
1. Endocrine therapy	Usually first line therapy in hormone receptor positive metastatic breast cancer.
2. Conventional cytotoxic therapy (Chemotherapy)	Act on dividing cells and kill cancer cells. Unfortunately also kills normal cells.
3. Targeted therapy	Targets a particular molecular function of cancer progression.
4. Bisphosphonates	In bone metastatic breast disease.

Table 1.1: Therapeutic options in metastatic breast cancer

Source: Smieliauskas, et al. (2014)

DeVita, Lawrence and Rosenburg (2015) defined metastatic breast cancer as stage IV disease that has spread beyond the breast, chest wall and the regional lymphatic drainage. Although there have been some literature case reports that breast can spread to any organ in the body, there are common sites of dissemination. Soni, et al. (2015) reported common distant sites namely: bone, liver, lungs, brain and pleura. The hierarchy is well demonstrated in Figure1.2 in the descending order.

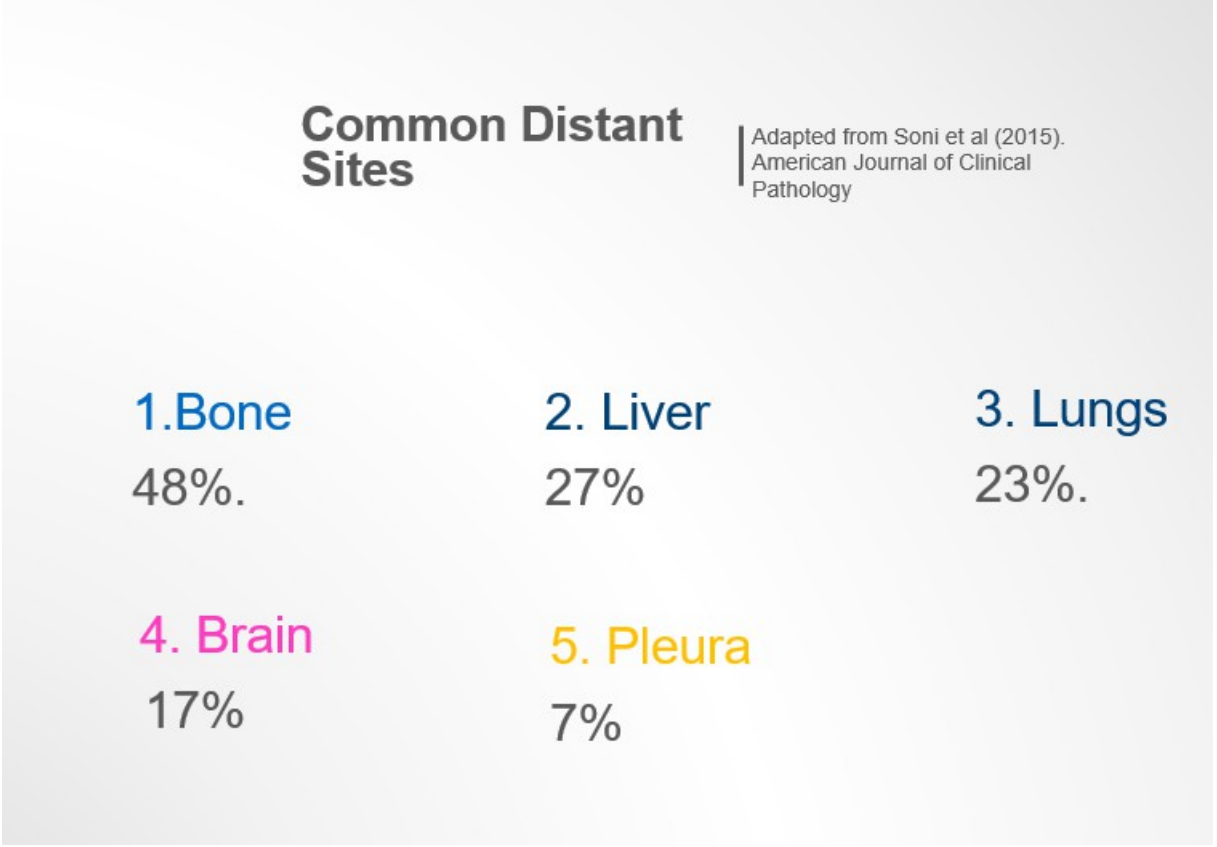

Figure 1.2: Common breast cancer metastatic sites

However, Kimbung, et al. (2015) further discussed that, even though they agree with Soni et al. (2015) on common sites of metastasis, the pattern of spread is influenced by breast cancer subtypes. For example, Kimbung, et al. (2015) argued that oestrogen receptor positive tumours turn to spread commonly to the bone and oestrogen negative tumours have a visceral spread pattern. The pattern of spread, Kimbung, et al. (2015) showed in Figure 1.3 that the frequency of site metastasis is based on molecular subtype. Bone is predominantly (about 50%) the common site of spread in all molecular subtypes. In addition, a Chinese study by Xiong, et al. (2018) reported bone metastasis to be between 60 -75% with Zhang, et al. (2010) also indicated bone metastasis in breast cancer is approximately 70%.

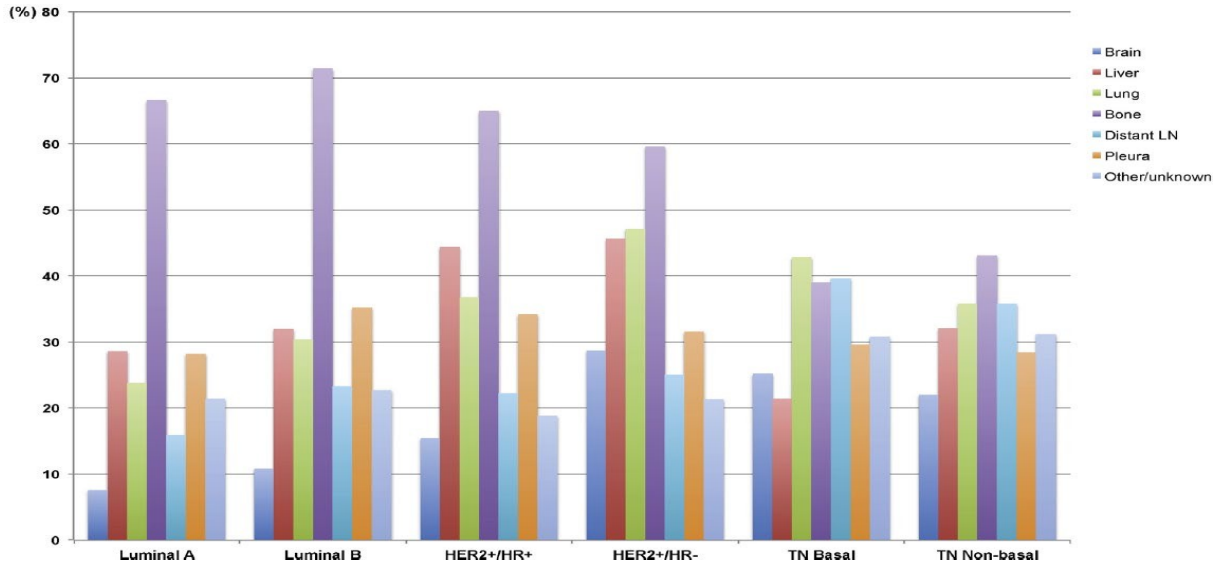

Figure 1.3: Frequency of common metastatic site by molecular subtype

Source: Kimbung et al. (2015).

Furthermore, Kimbung, et al. (2015) reported that in luminal A, luminal B, human endothelial receptor 2(HER2) positive/oestrogen positive and triple negative molecular subtypes the bone is the common site of metastasis of breast cancer. This is depicted above in Figure 1.3.

Development of new drugs

In the past few years, many new therapies in oncology were developed. In MBC, several targeted therapies have been approved by the Food and Drug Administration (FDA) (Table 1.2) The targeted therapies utilised in metastatic breast cancer are either HER2- targeted or non-HER2-targeted ones. Rugo, et al. (2010) showed that in MBC HER2 is amplified and over expressed in about 18-30% of cases.

Berghuis, et al. (2018) reported that the main challenge in cancer management is the escalation of healthcare costs especially in breast cancer. The authors argued that oncology accounts for 30% of the hospital expenditure. The development of new cancer drugs like trastuzumab has contributed to such escalation in costs. Furthermore, Tran and Zafran (2018) argued that there is a major challenge in balancing innovative drugs and the monetary cost of these drugs. This is relevant for healthcare decision makers, patients and the society.

The research & drug development resulting in these promising outcomes are a financial risk for the manufacturer. These costs are taken into consideration in the price calculation of the drug. The hot topic as Foster, et al. (2011), is that with the increasing incidence and mortality of MBC, the economic burden of treating it is huge and also controversial.

In low income like countries like South Africa, Govender, et al. (2016) also indicated the economic burden of cancer on the healthcare system.

Category	Generic name	Brand name	Class	Company	Patient population	Approval date
HER2-targeted therapy	Lapatinib	Tykerb	Dual HER1/HER2 inhibitor	GlaxoSmithKline	HER2+ mBC	2007
	Pertuzumab	Perjeta	HER2 inhibitor	Genentech	HER2+ mBC	2012
	Trastuzumab	Herceptin	HER2 inhibitor	Genentech	HER2+ mBC	1998
	Trastuzumab emtansine (TDM-1)	Kadcyla	HER2 – antibody-drug conjugate	Genentech	HER2+ mBC	2013
Other targeted therapy	Denosumab	Xgeva	RANKL inhibitor	Amgen	Bone mBC	2010
	Everolimus	Afinitor	mTOR inhibitor	Novartis	HR+, HER2 – mBC	2012
	Palbociclib	Ibrance	Inhibitor of CDK4 and CDK6	Pfizer	HR+, HER2 – mBC	2015
	Pamidronate, Zoledronic acid	Aredia, Zometa	Bisphosphonate	Chiron, Novartis	Bone mBC	1996, 2002

Table 1.2: Targeted drugs FDA approved in MBC

Source: Kang and Li (2016)

Research problem

Ataguba and Akazili (2010) reported that South Africa has a dual and highly inequitable health care system. The vast majority of people (68%) living in South Africa, for whom private medical insurance is unaffordable and inaccessible, are dependent on the government-funded public sector for healthcare services. According to Cancer Alliance (2018) trastuzumab is not available and not considered cost effective in SA public sector for the majority of breast cancer patients. It is for this reason that the Cancer Alliance group (2018) launched a campaign in 2016 to access trastuzumab in SA. With this background problem, this paper will try to answer the research questions outlined in the next section.

Research Question(s)

This paper will conduct literature search to evaluate the cost effectiveness of trastuzumab in MBC and attempt to answer the following research questions:

- Is it cost effective to use trastuzumab as first line therapy in MBC in South Africa?
- What is the acceptable willingness to pay threshold range for trastuzumab in South Africa?

Research objectives

The literature search on cost effectiveness of trastuzumab in MBC will be conducted to achieve the following objectives:

- To evaluate the cost effectiveness of trastuzumab as the first line treatment in MBC in South Africa.
- To recommend threshold value guidelines on expenditure of trastuzumab for South African healthcare.

In attempt to answer the above research questions, this study will review literature published in health economic studies on the cost effectiveness of trastuzumab in MBC. Subsequently discuss these studies in context to the SA context and make appropriate recommendations.

Theory and Practice of Cost Effectiveness of Trastuzumab in MBC

This Chapter will deliberate on theory and the practice of various economic studies published on cost effectiveness of trastuzumab in MBC.

The World Health Organization (WHO) cost effectiveness guidelines (2003) cost estimation of health care intervention can be divided into patients cost and non-patient costs. Patients costs are usually direct costs which are quantifiable like drugs, hospitalization, out-patient visits and laboratory tests. The non-patient costs refer to all other costs not associated with direct medical costs like administrative, marketing or prevention costs. The challenge has always been what economic model should be used in cost effectiveness studies. Angevine and Berven (2014) described three economic models to sensitize clinicians on the economic impact of different clinical interventions and decisions namely:

- Cost effectiveness analysis (CEA).
- Cost utility analysis (CUA).
- Cost benefit analysis (CBA).

Economic model	Advantage(s)	Disadvantage(s)
Cost effectiveness analysis (CEA)	• Measuring outcomes in 'natural units' like pain. Death etc. • Eliminates uncertainty. • sensitive effectiveness parameter can be chosen	• Generalizability. • Only interventions using the same clinical outcome can be compared
Cost utility analysis (CUA)	• Value in quality of life as primary end point. • Costs per quality adjusted life gained (QALY) commonly used. • Intervention for all diseases compared	• Less useful if primary endpoint is PFS/OS. • Controversyon QALY assumptions. • Limited QALY sensitivity.
Cost benefit analysis (CBA)	• Cost and outcomes combined in monetary units.	• Difficult to quantify life in monetary terms. • Rarely used in health economic evaluation.

Table 2.1: Advantages and disadvantages of CEA, CUA and CBA

However, the authors argued that there is no definitive method applies to all health situations. Advantages and disadvantages of each method are summarized in Table 2.1 above.

Cost effectiveness analysis

Claxon, et al. (2015) described CEA as a method that involves comparison of incremental cost effectiveness ratio of new intervention, which is usually costs more than the existing one. The comparison is with the known cost effectiveness threshold. This will indicate whether there are health gains in the new intervention or not. Therefore, the threshold represents the additional cost the new intervention will impose on the healthcare system to forgo QALY.

To calculate the ICER of the new intervention, Lidgren, et al. (2008) defined it as a ratio of the difference in the cost to the difference to the effect between two interventions. The formula is expressed as ICER= (Ca-Cb)/(Ea-Eb), where C is the cost and E is the effect. The effects are usually expressed in non-monetary units such as QALY.

Angevine and Berven (2014) reported that CEA is the most common model used in health care. As a principle this method has an advantage in that it measures the health outcomes in natural units like pain, death and quality of life gained. However, CEA has its drawbacks because of its generalizability and that only interventions using the same clinical outcome are compared.

Cost utility analysis

Furthermore, Angevine and Berven (2014) demonstrated that the use of CUA provides advantage in studies where the primary end point is quality of life in which QALY is commonly applied. QALY as described by Angevine and Beven (2014) as a unit measure from area of curve under health preference over time. This incorporates length and quality of life which is an advantage to avoid either using natural or monetary units as an outcome of value. However, the pitfalls in QALY are the controversy in the assumptions the model makes and the sensitivity of the model.

Cost benefit analysis

In contrast to CEA, CBA measures outcomes in monetary terms. The disadvantage is that it is a difficult approach in healthcare to measure patient's life using monetary terms. Therefore, it is rarely used in healthcare to evaluate economic outcomes.

This study will prefer applying the cost effectiveness approach to evaluate trastuzumab in MBC

In further discussion and support of the cost effectiveness and QALY analysis, the question of affordability is a challenge to back up the cost effectiveness of a drug in a disease. Several authors have investigated various viewpoints to address the question. Mustacchi and Generali (2017) indicated that WHO has defined the willingness to pay (WTP) by various countries as a threshold of at least 2-3 times of gross domestic product (GDP) per capita. For instance, Blank, et al. (2010) the United Kingdom (UK) uses the National Institute for Health and Care Excellence (NICE) with ICER per QALY from £20,000 to £30,000 and the United States of America (USA) from $50,000. This is determined in accordance with country specific GDP per capita. However, there is on- going debate about the threshold levels created whether they are low or high. Hence, Beishon (2018) in the latest spring Cancerworld newsletter reported on this ongoing controversy. Additionally, Beishon (2018) reported that the two of the major oncology societies in European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have developed tools to assist

oncologists, patients, regulators and governments in decision making on value of drugs. Scores are provided based on end points like overall survival, progression free survival and quality of life. The ESMO uses the Magnitude of Clinical Benefit Scale (MCBS) and ASCO uses Value Frame Work but the biggest debate is on the MCBS. It is against this background that Mustacchi and Generali (2017) argued that governments across the globe should determine what is affordable in line with cost effectiveness of the drug, survival outcomes, quality of life, the healthcare system and the economy of that specific country.

Literature Search: Methods and Materials

The literature search was conducted PubMed on (https://www.ncbi.nlm.nih.gov/pubmed/advanced). Using the advanced search in PubMed, the MESH (Medical Subject Headings) search terms were: "Cost Effectiveness AND Trastuzumab AND Metastatic Breast Cancer". The initial search yielded 70 articles. The inclusion and exclusion criteria as shown in Table 2.2, yielded 5 articles (Table 2.3) that fitted the inclusion criteria of the study.

Criteria	Inclusion	Exclusion
1. Time period	From 01-01-2008 to 31-12-2017	Before 01-01-2008 and after 31-12-2017
2. Language	Articles published in English language	Non- English published articles
3. Article type	Original Health economics on cost effectiveness with outcomes on ICER/QALY on trastuzumab.	Review articles and economic outcomes other than the ones mentioned in the inclusion criteria.
4. Treatment setting	First line trastuzumab treatment in metastatic breast cancer	Second/third line treatment lines of MBC
5. Type of anti-HER2 drug	Trastuzumab with or without chemotherapy.	Studies on chemotherapy only in MBC. Other anti-HER2 drugs like lapatinib, pertuzumab and TDM-1

Table 2.2: Cost effectiveness of trastuzumab in MBC literature search inclusion and exclusion criteria

Further search was conducted through Cochrane library (https://www.cochranelibrary.com/advanced-search). In this search we also used MESH terms "Cost Effectiveness AND Trastuzumab AND Metastatic Breast Cancer". In addition, we created search limits as follows, content type (trials), publication years (2008 to 2018) and lastly the Cochrane group selection. This search initially yielded 16 articles. Using the inclusion/exclusion criteria above, one article was finalised from the Cochrane search. We further conducted google search (https://www.google.com/search?q=Costeffectiveness+Analysis+of+Trastuzumab+in+the+Treatment+of+Metastatic+Breast+Ca ncer&ie=utf-8&oe=utf-8&client=firefox-b) using "Cost effectiveness of trastuzumab in metastatic breast cancer" Yielded 287 000 results. However, decided to select the scholarly articles which were four. Only one article fitted the inclusion/exclusion criteria.

MESH terms: "Cost Effectiveness and Trastuzumab and Metastatic Breast Cancer"	**PubMed articles**	**Cochrane articles**	**Google search**
Initial search	70 articles.	16 articles	4 scholarly articles chosen
Final articles that met criteria	4 articles	1 article	1 article

Table 2.3: PubMed and Cochrane libraries search articles

Health Economics Studies

The economic studies below will follow the sequence as depicted in Table 2.4. Please note that the ICER/QALY values will be in approximated euros based on the current exchange rates in annexure 1.

Study 1

To evaluate the cost effectiveness of trastuzumab in MBC, Poncet, et al. (2008), conducted a prospective French (Lyon) study, on cost effectiveness analysis on the use of monoclonal antibody trastuzumab in MBC. Group A received a combination of trastuzumab and chemotherapy (paclitaxel) as first line treatment for MBC in 4 predefined centres. Group B received chemotherapy of any choice by the investigator in 6 control centres. In comparison of Group A and Group B, the additional cost per saved year of life was expressed as incremental cost effectiveness ratio of €15,370/QALY.

Study 2

In another French (Marseille) study by Perez-Ellis, et al. (2009) published the paper on the cost effectiveness analysis of trastuzumab in HER2 over-expression in MBC. This study of 47 patients was conducted in a French oncology department on homogeneous population with HER2 over expression in MBC It was a retrospective study designed as a "before" and "after" trastuzumab era. In essence, the authors made an economic evaluation of trastuzumab administration just before and after introduction of trastuzumab into clinical practice. All patients received standard chemotherapy but the first 19 patients did not yet receive trastuzumab but chemotherapy only (taxane and/ anthracycline), whereas the following 28 patients received trastuzumab (4 mg/kg intravenous (I.V.) loading dose of trastuzumab followed by an I.V. infusion of 2 mg/kg/week until progression.

Perez-Ellis, et al. (2009) employed ICER to conduct cost effectiveness analysis of trastuzumab in metastatic breast cancer. The ICER per QALY for this study was €17,800.

Study 3

In Brazil, Bandeira, et al. (2015) conducted a study on 1000 women over the age of 50 with HER2 over-expression in MBC. They performed a CEA of trastuzumab in combination with chemotherapy (paclitaxel or docetaxel) and chemotherapy alone as first line treatment of MBC. The study was conducted over 48 months. They wanted to estimate the costs and the health benefits of trastuzumab with chemotherapy and chemotherapy alone. This study was conducted according to the Brazilian health system perspective using ICER/QALY.

The ICER/QALY was $1565.49 in the trastuzumab docetaxel arm and $12,573.62 in the trastuzumab paclitaxel arm. This meant trastuzumab docetaxel is more cost effective than trastuzumab paclitaxel even though they both cost effective from the Brazilian perspective.

Study 4

In the Swedish study by Lidgren, et al. (2008), cost effectiveness of trastuzumab and chemotherapy (docetaxel) versus chemotherapy alone (docetaxel) in MBC was performed. This study included women of 65 years with over expression of HER2. According to the Swedish health guidelines all patients with breast cancer had to test for HER2 expression using immunohistochemistry (IHC) and Fluorescence in Situ Hybridization (FISH) analysis for IHC 2+ and IHC3+ disease. It is for this reason that the medical costs for trastuzumab did not only include out-patient and in-patient costs but also the IHC and FISH tests costs.

In the FISH strategy the ICER/QALY in the trastuzumab and chemotherapy was 561 207 SEK (approximately €53,961).

Study 5

Diaby, et al. (2017) conducted a study in Mexico to evaluate the economic outcomes and sequencing of HER2 expressed MBC. The aim of the study was to compare the public and private sector perspective of using first to third line treatment anti-HER2 options in MBC. The first line setting treatment was the use of trastuzumab and docetaxel followed by other treatment lines of trastuzumab and lapatinib and trastuzumab/pertuzumab/docetaxel in MBC. However, due to exclusion criteria of other anti-HER2 therapies in this paper only the trastuzumab and docetaxel sequence will be evaluated as first line treatment in MBC. Patients were followed up weekly over their life expectancy. The medical costs included medical visits, drug acquisition, supporting drugs like G-CSF, imaging, laboratory tests, adverse events management and end of life care. In this study, the sequencing that included trastuzumab/docetaxel was cost effective with the ICER/QALY of $32,904.66 from a public sector perspective.

Study 6

In Greece, Athanasakis, et al. (2011) investigated the cost effectiveness of adding trastuzumab to docetaxel monotherapy to women with HER2 positive MBC. The data on effectiveness was derived from administering docetaxel 100mg/m2 every 3 weeks, with or without trastuzumab 4mg/kg loading dose followed by t2mg/kg until disease progression. The outcomes of this study considered addition of trastuzumab to docetaxel to be cost effective in Greece from third party payer perspective at €41.811.13/QALY.

Author	Country	Treatment Regimen	Cost Effectiveness Ratios	Conclusion
Poncet, *et al*,2008	France	Group A(T+P) versus Group B(P only)	ICER €15, 370/QALY with T+P	Cost effective and affordable by French health system
Perez-Ellis,*et al*, 2009.	France	T+A/P A/P alone	ICER €17,800/QALY in T+A/P	Cost effective despite high costs
Bandeira,*et al* 2015	Brazil	Trastuzumab with P/D	ICER of €1 363.13/QALY in T+A and €10 958.19/QALY in T+P	Both strategies cost effective
Lidgren,*et al* 2008	Sweden	T+D	ICER/QALY €53,961	Cost effective
Diaby,*et al* 2017	Mexico	T+D strategy	ICER/QALY €28 679.95	Cost effective in the public sector
Athanasakis,et al 2011	Greece	T+D versus D only	ICER/QALY €41.811.13	Cost effective from third payer perspective

Table 2.4: Summary of studies on Cost effectiveness of trastuzumab in metastatic breast cancer.

A: Adriamycin, C: Chemotherapy, D: Docetaxel, ICER: Incremental cost effectiveness ratio, P: paclitaxel, T: Trastuzumab

Discussion, Conclusion and Recommendations

Discussion

The Cambridge dictionary (2018) defined cost effectiveness as good value for money paid for a particular activity. The benefits should at least be worth what is paid for. In healthcare, WHO reported that cost effectiveness estimates the costs and health gains of alternative health interventions. The WHO argued that this will assists policy makers in allocation of resources to yield the greatest improvements in different health situations. The estimation of costs and health benefits gives guidelines to minimize expenditure and maximize outcomes in tight health budgets.

Mariani and Fernandes (2014) defined WTP as an economic term to maximum amount of money one is prepared to pay or sacrifice in order to receive goods or services. In medicine this is used to assess the value of health benefits. The WHO has recommended the WTP by various countries as a threshold of at least 2-3 times of GDP per capita. Marseille, et al. (2014) reported that GDP per capita is the most common used approach by the WHO to attempt to solve the problem of cost effectiveness as compared to the benchmark and league tables approaches.

The GDP per capita will be different from country to country. Therefore, what is cost effective will be determined by threshold value based on GDP per capita. This notion was supported by Sarfaty, et al. (2018) who believed that the probability of cost effectiveness of a drug is also influenced by the WTP of various countries. Western countries will have higher threshold values based on the GDP per capita. Sarfaty, et al. (2018) demonstrated how cost effectiveness is influenced by threshold values from various countries in Canada, Australia, USA and the UK. This is illustrated in Figure 3.1 below. The WTP depends on GDP per capita and cost effectiveness correlates to WTP/QALY and this shows the differences in healthcare systems worldwide. The USA will have the highest WTP as compared to the lowest threshold WTP of countries like UK.

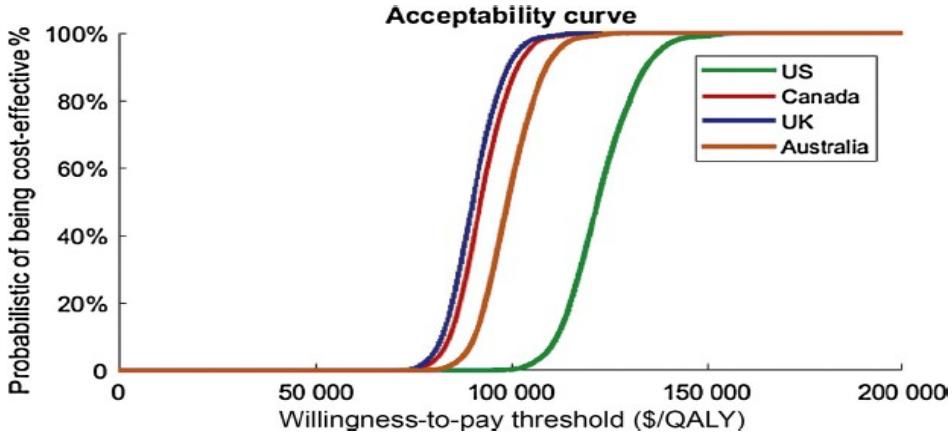

Figure 3.1: Cost effectiveness probability curves in US dollars

Source: Sarfaty et al. (2018)

The World bank (2016) has reported that western countries have the highest GDP worldwide. The GDP for US, UK and France are about 5-7 times higher than the so called BRICS states (Brazil, Russia, India, China and South Africa as shown in Table 3.1. SA with an approximate GDP of R114,000 can be considered a typical BRICS state with the GDP of Brazil (R166,000), Russia (R169,000), China(R105,000) and India (R28,000) being close by.

This Chapter will assume the current USD/ZAR/Euro exchange rate provided by Bidvest (see annexure1). Amounts are rounded off to the nearest thousand.

The WTP by western countries like USA, UK and France is documented as shown in Table 3.1. However, the WHO 2-3 times GDP per capita recommendation is used to extrapolate on possible WTP of other countries. These figures are also rounded off to the nearest thousand to make it easier to read.

Country	GDP/capita (USD/ZAR)	WTP (ZAR)
South Africa*	**7,500**/114,000	***228,000-342,000***
France	**42,000**/639,000	960,000-1, 200,000
United Kingdom	**41,600**/632,000	400,000-600,000
United States of America	**52,200**/793,000	760,000-2,200.000
Russia*	**11,100**/169,000	***340,000-500,000***
Brazil*	**10,900**/165,000	***330,000-500,000***
China*	**7,000**/105,000	***210,000-315,000***
India*	**1,900**/28,000	***57,000-85,000***
Sweden	**51,600**/762.000	***R310.000 to R500,000***

Table 3.1: GDP per capita by country and WTP

*: BRICS countries Exchange rate according to Bidvest (2018/09/18): rounded off

Source: Tradingeconomics.com: World Bank (2016)

The scientific view to evaluate the cost effectiveness of trastuzumab, the ICER/QALY and the WTP threshold was used. In case of missing data, the WHO recommendations are assumed. Both Poncet, et al. (2008) and Perez-Ellis, et al. (2009) were in agreement on the cost effectiveness of trastuzumab in MBC. This was acceptable based on the WTP threshold values from R960,000, R1,200,000. The ICER/QALY of these studies was lower than the expected range. Therefore, trastuzumab was considered cost effective.

Lidgren, et al. (2008) considered the use of trastuzumab in MBC to be cost effective at R916,000/QALY even though this was above the estimated WTP in Sweden of R310 000 to R500 000.

To compare with BRICS countries, in Brazil, Bandeira, et al. (2015) concluded that the treatment is cost effective with the WTP threshold range between R330,000-R500,000. Russia does not have published studies on use of trastuzumab in MBC. However, Kolyadina, et al. (2018) published online, has demonstrated the use of trastuzumab biosimilar (Herticad) to be economically reasonable in the neo adjuvant breast cancer treatment with a cost drop of 75%.

Times live news (2017) reported that in India the price was dropped to R110,000 per year for trastuzumab which was a 75% drop in price. This was after the completion commission in that country ordered the manufacturer to produce generics to make drug affordable. The estimated WTP in India is R57,000-R85,000 then trastuzumab was considered cost effective.

In China, Chen, et al. (2009) considered trastuzumab to be cost effective in the adjuvant setting not in MBC with ICER/QALY of R122,000. This study used the WHO GDP/capita recommendation. Then the estimated WTP is R210,000-R315,000 which makes trastuzumab cost effective although this was in the adjuvant treatment setting of breast cancer.

In SA there is no data available or studies conducted on cost effectiveness of trastuzumab in MBC. Therefore, as Govender, et al. (2016) indicated various aspects need to be considered, such as the South African WTP and secondly the cost effectiveness. In order to estimate the WTP and cost effectiveness further countries like Mexico with a similar funded health system are considered.

Diaby, et al. (2017) concluded cost effectiveness for Mexico with the ICER per QALY of R50,000. National Centre for Health Technology Excellence (CENETEC) in Mexico cost- effectiveness threshold is set at 1 per capita GDP for drugs entering the healthcare system. This is even stricter than the WHO recommendation of 2-3 times per capita. If the present GDP per capita of Mexico is R125,000, their WTP is the same amount, which then puts trastuzumab to be acceptable.

In SA, Govender, et al. (2016) estimated the cost of trastuzumab treatment to be R500, 000 per year. This falls above the estimated WTP range of R228,000-R342,000. Trastuzumab is presently only considered cost effective in the South African Military Health Services (SAMHS) as a generic (Herclon) and in the private sector as originator (Herceptin).

Ataguba and Akazili (2010) argued that this is due to the imbalance in the healthcare funding of SA. For instance, in 2008 private medical aid spent R10 000 per member compared to R1 900 in the public sector, whilst the public sector constitutes 68% of the population. In SA, trastuzumab is currently not funded in the public sector.

SA is still predominantly (68%) the state type healthcare system as reported above by Ataguba and Akazili (2010). The challenge to fund drugs like trastuzumab becomes high if funding is dependent on the provider as government especially if the budgets are stretched in the public sector. It is for this reason that in SA there is an ongoing discussion on cost effectiveness. Different health providers have found different solutions for this problem. India for example introduced generic trastuzumab and this dropped the price by 75% at R110,000 per year. The SAMHS also provides trastuzumab in the generic form and this has dropped price by 74% at R128,000 per year. Mexico negotiated different forms of price reduction. Further direct cost might be reduced by choosing a different application form of trastuzumab like subcutaneous injection.

The WTP on trastuzumab in breast cancer treatment in SA has not been evaluated. However, Meyer-Rath, et al. (2017) conducted WTP study in HIV prevention and treatment based on country's committed budget to HIV. The authors found a WTP range of R227,980-R341,970. Govender, et al. (2016) estimated the cost of trastuzumab at R500,000 per year at dose of 6mg/kg on average 70kg patients. The estimation was based on the private sector where trastuzumab is funded for. Even though this puts the cost of trastuzumab outside the estimated HIV-WTP it is considered cost effective in the SA private health care market.

To answer the question of whether trastuzumab is cost effective in MBC in this country, the estimation, based on the literature review, is that generally a cost effectiveness of trastuzumab in the first line therapy of MBC in the western world is accepted.

However, with the current estimated treatment cost the first line treatment of trastuzumab in MBC can't be considered cost effective in SA public sector. This is based on the cost of trastuzumab falling outside the range of WTP in SA by 32% (R158,000).

Possible weaknesses of the review

There are possible limitations in the CEA of trastuzumab of this paper. In SA there is no data available or studies conducted on cost effectiveness of trastuzumab in MBC. The review depended largely on retrospective studies conducted in other countries, especially the western countries to determine the cost effectiveness of trastuzumab. Nevertheless, this review utilises the WHO recommendation of WTP being 2-3 times of the country GDP/capita. Using this approach, it is extrapolated that trastuzumab in SA should be in the range of R228,000-R342,000 to be considered cost effective.

Though the use of trastuzumab contributes to increasing medical costs, the estimation, based on the literature review supports the use. But in the SA health sector, there are no economic evaluation studies on treatment in MBC to provide more reliable data. However, if such studies were to be conducted, the types of direct medical costs based on the study cost effectiveness, the cost of the drug (trastuzumab) itself, the inclusion of diagnostic tests and imaging, hospitalization and in and out patients a rough estimation should be evaluated according to

the French studies by Poncet, et al. (2008) and Perez- Ellis, et al. (2009).

Another possible weakness which could assist in determining whether it is cost effective for SA public sector to use trastuzumab, is the possible cost reduction negotiations between Roche and SA government. However, the content of the negotiations is unknown. This is usually common practice as reported by Leopold, et al. (2013) that these kind of negotiations are kept confidential hence the lack of proper documented data on such deals.

Depending on who funds, regulates or provides the healthcare system, Wendt, et al. (2009) described financing as one of the three dimensions of healthcare systems besides regulation and service provision. South Africa is still predominantly (68%) the state type healthcare system as reported above by Ataguba and Akazili (2010). The challenge to fund drugs like trastuzumab becomes high if funding is dependent on the provider as government especially if the budgets are stretched in the public sector. It is therefore difficult to compare the SA healthcare system with other western countries and the BRICS countries in WTP for such drugs. It is for this reason that in South Africa there is an on-going discussion and pilot studies to move to National Health Service due to the imbalances in the healthcare provision and funding in the country.

Conclusion

This paper reviewed the literature on the cost effectiveness of trastuzumab in MBC to answer the question: 'Is trastuzumab cost-effective in the treatment of MBC in the South African health sector'.

In the western countries like France, UK and Sweden trastuzumab has been shown to be cost effective in MBC. In addition, other BRICS countries like Brazil and India have demonstrated the cost effectiveness of trastuzumab. Other countries like Mexico considered trastuzumab to be cost effective in the public sector after pharmaceutical price reduction has come into place. However, in SA it is currently not considered to be cost effective in the public sector which constitutes the majority population in the country. In the private/military sector the trastuzumab treatment is offered even though the price of trastuzumab is above the estimated WTP based on WHO recommendation.

Recommendations

1. Initial research in South Africa should determine the direct and indirect cost in oncological treatment in the public sector.

2. Based on our assumptions of WTP and cost per treatment year the estimated price for trastuzumab to be considered cost effective is R 228 000 – R 342 000.

3. Encourage acceleration of price reduction negotiations between drug manufacturers and the government.

4. Introduce biosimilars or generics if necessary.

5. Encourage South African health policy makers, clinicians and possibly patients to participate in further cost evaluations.

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