Pharmaceutical Regulatory Affairs: Open Access

Ramirez-Torres et al., Pharmaceut Reg Affairs 2013, 2:2
DOI: 10.4172/2167-7689.1000113

Review Article Open Access

Cost-Effectiveness Analysis of Neoadjuvant Chemotherapy with Intensive Dose of Epirubicin and Different Cycles in Patients with Locally Advanced Breast Cancer: 4 Fe_{100}c Vs. 6 Fe_{100} C

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Abstract

Introduction: There are different combinations of neoadjuvant chemotherapy (NCT) to treat locally advanced breast cancer (LABC); treatment with cytostatics drugs make it a costly concern, by establishing economic differences in the consumption of health care resources.

Objective: To compare the cost-effectiveness of two NCT strategies.

Patients and method: it was made a cost-effectiveness analysis (CEA) of two treatment schemes (4FE_{100}C vs. 6FE_{100}C) in patients with clinical stage III breast cancer, each cohort included 48 patients.

Effectiveness parameter: pathologic complete response (pCR).

Differential cost: incremental cost-effectiveness ratio (ICER) using a Markov's model. Results are expressed in terms of incremental cost per extra unit of effectiveness. Costs were expressed in Mexican (MXN) pesos ($) as of 2005; these were calculated under the perspective of public health care system (SSP, for its acronym in Spanish) denominated IMSS, with a 3 to 4 years analytical horizon. In order to determine the robustness of the results, a sensitivity analysis was carried out by modifying only the medical direct costs with a 3% discount rate.

Results: The use of 6FE_{100}C offered greater effectiveness compared against 4FE_{100}C; the medical direct cost of only the cytostatic drugs for NCT with 6 FE_{100}C and 4 E_{100}C generated a cost per case of $30,467.00 MXN (€ 2,343.61) and $18,004.00 MXN (€ 1,384.92), respectively. The greatest unit price was given by epirubicin. The CEA demonstrated that the cost-effectiveness (C/E) was greater with 6 FE_{100}C and the incremental cost-effectiveness ratio (ICER) showed that it was necessary to pay $11,765,925.42 MXN (€ 905,071.20) because it tells us how much it is paid additionally for every extra unit of effectiveness (pCR) which assumes 6 FE_{100}C in front of 4 FE_{100}C. The sensitivity analysis performed shows the robustness of the results.

Conclusion: The 6 FE_{100}C scheme is the strategy with better cost-effectiveness ratio and is the most efficient in the short run for treating LABC.

Keywords: Cost-effectiveness; Neoadjuvant chemotherapy; Advanced breast cancer

Introduction

Breast cancer is a health concern in Mexico, for various reasons: most of the cases are diagnosed at advanced stages (40% to 60%), the number of cases and the mortality rate of this pathology have steadily increased in the course of time in women older than age 25 years from 2000; [1-3] thus, it is necessary to establish a multimode treatment including a neoadjuvant chemotherapy (NCT) which is the first-choice treatment to treat the advanced breast cancer. Different regimens of NCT have been used, most oncological centers have implemented anthracyclines -containing regimens [4-14] and recently the use of taxanes [15-17].

The treatment of locally advanced breast cancer (LABC) according to the various NCT assays makes it a costly concern since there are significant economic differences in the consumption of healthcare resources. The choice of treatment depends upon many factors, such as available resources, drug costs and the physician's preference.

Various economic assessment studies [18,19] have proved the efficacy of epirubicin with intensive dose (100 mg/m^2) in the adjuvant treatment of patients with early breast cancer; they point out that this anthracycline has demonstrated its efficiency in terms of cost-effectiveness ratio. However, we do not have information of cost-effectiveness related the NCT with FEC.

The protocol only differs from the number of cycles used (4 vs. 6) with fixed intensive dose (100 mg/m^2) of epirubicin. Our knowledge of the pharmacoeconomic study on FE_{100}C as a neoadjuvant therapy is limited. In order to analyse the costs and medical benefits of this therapeutic strategy in a Mexican healthcare third-level hospital, this study has been performed; the objective was to carry out an incremental cost-effectiveness ratio analysis (ICER) of epirubicin with

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Received September 11, 2013; **Accepted** October 28, 2013; **Published** October 31, 2013

Citation: Ramirez-Torres NMC, Herrera-Abarca Jorge EDC, Chavez-Carbajal Jose FMC, Hernandez Valencia MDC (2013) Cost-Effectiveness Analysis of Neoadjuvant Chemotherapy with Intensive Dose of Epirubicin and Different Cycles in Patients with Locally Advanced Breast Cancer: 4 Fe_{100}c Vs. 6 Fe_{100} C. Pharmaceut Reg Affairs 2: 113. doi:10.4172/2167-7689.1000113

intensive dose (100 mg/m^2) using 6 cycles of 5-fluorouracil, epirubicin and cyclophosphamide ($FE_{100}C$) against 4 cycles of $FE_{100}C$ delivered as NCT in patients with LABC.

Patients and Method

Mexican institute of social security (IMSS)

IMSS is a public decentralised agency with legal personality and its own assets with involving of the public, social and private sectors. Its role is to provide services related to economic, social and medical benefits foreseen in regimens: mandatory, voluntary and social solidarity; [20,21] IMSS provides social security to 44% of the Mexican population as a whole [21].

Population of study

The trial was performed in female population in the High-Speciality Medical Unit (UMAE, for its acronym in Spanish) of Gyneco-Obstetrics Hospital No. 3, NMC La Raza, IMSS; study non-randomised, retrospective with historical control (4 $FE_{100}C$) and treatment group (6 $FE_{100}C$). The choice of patients was in patients with high risk of relapse according AJCC 2002: T3-4 with N0-2, any T with N2-3 [22].

Screening criterion

A total of 96 patients were screened through a consecutive sampling, grouped in two cohorts: 4 $FE_{100}C$ and 6 $FE_{100}C$. Inclusion criteria: >18-year-old woman, stage-III breast cancer; histopathological diagnosis of infiltrating carcinoma. In the treatment group (6 $FE_{100}C$), patients signed the Informed Consent Letter. Exclusion criteria: patients with hematological and non-hematological severe toxicity; irregular treatment in dose or in time or with cardiovascular clinical manifestations.

Under the healthcare provider's perspective corresponding to the public healthcare system (SSP) registered as Mexican Institute of Social Security (IMSS), who utilized healthcare services (either ambulatory or inpatient). A cost-effectiveness-analysis (CEA) was carried out.

This trial only contemplates the short-term analysis of medical direct costs in patients with LABC in which the administering of 6 $FE_{100}C$ is compared against 4 $FE_{100}C$ as NCT; in addition, the cost associated to treatment of severe toxicity was quantified in each treatment group. Once the neoadjuvant treatment ended in both groups, surgery was performed. The study analysis comprises the period of time from January 2003 to December 2007.

Data Analysis

Effectiveness of treatment

The effectiveness of treatment was assessed according to the chemotherapy scheme chosen for the short term. Cytostatic drugs were administered as neoadjuvant treatment and the effectiveness was assessed with the following criteria:

1. Pathologic complete response (pCR), was defined as the complete disappearance of primary breast tumor and axillary nodes; histological findings of malignant, non-invasive cells (carcinoma in situ) were included in the pCR category [23].
2. Objetive response rate (ORR), includes the sum of both complete response (CR) and partial response (PR). CR is defined as the total disappearance of tumour; PR corresponds to the decrease by at least 50% of the tumour size measured as the sum of the products of the two major perpendicular diameters of the tumour, without any evidence of new injuries.

The effectiveness was understood as a measure of (short-term) intermediate result; the number of pCR and ORR was calculated as the sum of responses achieved and detected in every year. In this trial, data on effectiveness and tolerability have been taken from clinical data of the local study and were incorporated to the CEA. Gained years of life (GYL), which is a final response (long-term) measure, were not contemplated in this study.

Pharmacoeconomic analysis

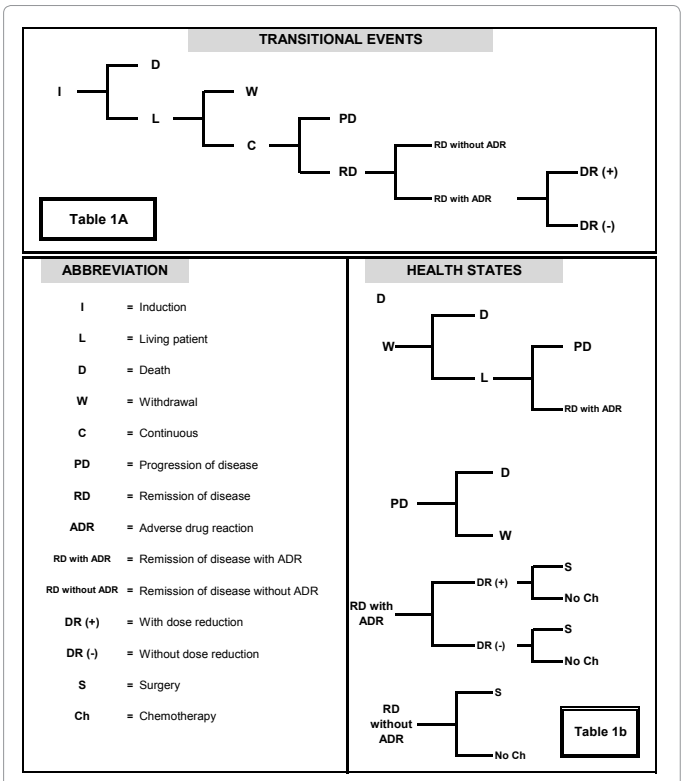
The cost-effectiveness analysis (CEA) is the most common way to carry out any economic assessment of medical interventions aimed to determine which interventions are a priority to maximise the benefit produced by the economic resources available [24-28]. The parameter that was taken into account for the pharmacoeconomic assessment was the ICER, where the parameter of effectiveness varied for each type of treatment: pCR percentage.

Medical assistance cost analysis

In order to quantify the costs, the perspective of the health care-services (IMSS) provider was taken. Data of unit costs of drugs come from the IMSS Basic Schedule as of July 2005 [29] and of the Institutional Supplying System (SAI, for its acronym in Spanish) as of October 2005 [30], the costs are calculated for every drug in a unit fashion, per total dose and per cycle, which were expressed in Mexican (MXN) pesos ($) as of 2005 and its equivalence in Euros as of 2005; data of costs were focused on cost-effectiveness.

Temporary horizon, discount rate and sensitivity analysis

In the short-term model, results of the therapeutic responses to 4 and 6-cycle chemotherapy were assessed with a 3% discount rate for costs. After not having a consensus on whether the health care benefits



Graph 1: Markov's cycle models for patients with locally advanced breast cancer: 1A Transitional events. 1B Health states.

must be discounted or on what discount rate it is needed to be applied, no modifications were performed to the effectiveness, a univariate sensitivity analysis was carried out by modifying only the costs. The temporality corresponded to 3 and 4 years.

Model Design

Health states were defined by the presence or non-presence of four transition events: 1) death/survival, 2) withdrawal/continuation of treatment, 3) progression/remission of disease and 4) reduction/non-reduction of dose (Graph 1).

From the first state, the patient can go through the state of withdrawal or through the states of progression/non-progression of the disease, in the event of non-progression; patients are moved to the states of remission with or without reduction of dose. The withdrawal may occur by either death, progressive disease (PD) or severe adverse drug reaction (ADR).

Each intervention was analysed through a Markov's model, where patients were cyclically moving through five mutually-exclusive health states: a) death, b) withdrawal, c) progression, d) remission with ADR and e) remission without ADR (Graph 1).

In the first Markov's cycle, all patients leave from the state of induction, with a probability of 1; they are candidates for first-line chemotherapy (any of the two options), during the first cycle, patients could die (D) or stay alive (AL); surviving patients could have PD or remission of disease (RD) with severe toxicity; thus, they were withdrawing (W) from the treatment or could continue (C) with dose reduction (DR+) or without dose reduction (DR-) (Graph 1).

Costs of diagnosis and medications of neoadjuvant chemotherapy		
Medical resources and services Study group	Unit cost Pesos (MXN)	Unit cost Euros (€)
a. Diagnosis Breast biopsy		
Core-cut needle biopsy	604.00	46.46
Incisional biopsy	727.00	55.92
Extension studies:		
Bone radiography scans	367.00	28.23
Liver ultrasound	311.00	23.92
Mammography	213.00	16.38
b. Medications Pre-chemotherapy:		
Dexamethasone Amp. 8 mg	11.03	
Ondansetron Amp. 8 mg	89.42	
Ranitidine Amp. 50 mg	0.62	
Total cost: 6-cycle FEC	Average 606.42	46.64
Total cost: 4-cycle FEC	Average 404.28	31.09
Chemotherapy:		
5-Fluorouracil Amp 250 mg	11.96	
Cyclophosphamide Amp 500 mg	72.98	
Epirubicin Amp. 50 mg	1,103.43	
Total cost: 6-to-8-cycle FEC	Average 30,467.00	2,343.61
Total cost: 4-cycle FEC	Average 18,004.00	1,384.92
Post-chemotherapy:		
Tropisetron Cap. 5 mg	146.29	
GranisetronTabl. 1 mg	74.91	
OndansetronTabl. 8 mg	56.21	
Ranitidine I Tabl. 150 mg	0.13	
Total cost: 6-cycle FEC	Average 1,553.82	119.52
Total cost: 4-cycle FEC	Average 1,116.54	85.88

Costs expressed in Mexican (MXN) pesos ($) as of 2005, according to the perspective of public healthcare system with insured population denominated Mexican Institute of Social Security (IMSS).

Table 1: Unit cost of medical services and resources per study group that estimates the cost-effectiveness model for patients with locally advanced breast cancer (stage III) in IMSS.

Costs of monitoring , surgical and toxicity		
Medical resources and services Study group	Unit cost Pesos (MXN)	Unit cost Euros (€)
c. Monitoring		
Oncologist's consultation	771.00	59.30
Hematic biometry	77.00	5.92
Renal function test	77.00	5.92
Liver function test	245.00	18.84
Chemotherapy application	340.00	26.15
d. Surgery:		
Modified radical mastectomy	11,671.00	897.76
Oncologist surgeon's consultation	771.00	59.30
Anaesthesiologist's consultation	771.00	59.30
Internist's consultation	771.00	59.30
Electrocardiogram	356.00	27.38
Pathologist's consultation	771.00	59.30
e. Toxicity		
Filgrastim	1461.76	112.44
(Material) transfusion	1,003.00	77.15
Total cost: 6-cycle FEC	93,675.50	7,205.80
Total cost: 4-cycle FEC	7,324.40	563.41
Grand total		
FEC (6 cycles), n=48	$2,757,571.38	212,120.87
FEC (4 cycles), n=48	$1,780,999.57	136,999.96

Costs expressed in Mexican (MXN) pesos ($) as of 2005, according to the perspective of public healthcare system with insured population denominated Mexican Institute of Social Security (IMSS).

Table 2: Unit cost of medical resources and services per study group that estimates the cost-effectiveness model for patients with locally advanced breast cancer (stage III) in IMSS.

Patients with RD had different types of responses as primary endpoints: pathological complete response (pCR), pathological partial response (pPR) and stable disease (SD). Patients with grade-3 toxicity (G3) had a delay of the following chemotherapy cycle up to the solution of toxicity; once the toxicity was overcome, they moved to the RD state without dose reduction. Once this phase was overcome, surviving patients could continue with PD or RD with DR(+) or without DR(-).

In the second cycle of the model, patients who withdrew the treatment for severe ADR or had PD could receive second-line chemotherapy and not undergo surgery; on the other hand, patients with RD with or without DR could undergo surgery for loco regional control. These two states could repeat the same four transitional events and access the other five health states for a new cycle.

Use of Resources and Cost Calculation

A total cost analysis was performed on both therapeutic arms, by identifying and quantifying the respective use of health care resources; direct medical costs were integrated into five major groups: a) the ones related to the diagnosis; b) the ones linked with drug administration; c) monitoring costs, d) surgical costs and e) costs derived from toxicity Tables 1 and 2.

1. Group related to the diagnosis. Biopsies were made with tru-cut needle biopsy or incisional- biopsy; cabinet studies, such as chest X-rays, bone radiographic scans or bone scintigraphy and liver ultrasound were included before starting the NCT. The use of mammography was not routine.

2. Group related to drugs. It was divided into three subgroups: pre-medication, chemotherapy and post-medication. Within the first subgroup, medication was contemplated previous to chemotherapy: dexamethasone, ondansetron and ranitidine; the second subgroup included costs of cytostatic drugs ($FE_{100}C$) and in the third subgroup, it corresponded to post-chemotherapy medication: granisetron, tropisetron, ondansetron, ranitidine and prednisone at the physician's criterion.
3. Group linked with monitoring costs. Complementary tests were included, such as hematological studies, visits to the specialist where the oncologist determined the continuation or non-continuation of treatment.
4. Group related to surgery. Costs related to surgical procedure, medical consultation with the surgical oncologist, preoperative (anaesthesiologists and internists) assessments and thus as pathologist's assessments.
5. Finally, the group linked with the toxicity of cytostatic drugs; four types of severe toxicity were considered: costs generated by G3 neutropenia, G2 anemia that deserved blood transfusion; severe nausea/vomiting and infection deserved hospitalization.
6. Total cost was calculated as the summation of the unit cost of each therapeutic procedure multiplied by the number of cycles given, the updating rate was applied from the resulting summation (3% discount).

Calculation of Effectiveness and Differential Cost Results

The results of the model were expressed in terms of the effectiveness got by clinic assay (4- $FE_{100}C$ vs. 6-$FE_{100}C$; differential costs are expressed in terms of the incremental cost-effectiveness ratio (ICER). The ICER is the quotient between the difference of costs and the difference of effectiveness between the two groups studied and is expressed in terms of the short-term incremental cost per extra unit of effectiveness (pCR).(31,34). pCR, unit cost of each medication, unit cost of speciality consultation, mean cost-effectiveness (MCE) and ICER were recorded following the NCT.

Results

An economic assessment of two schemes of treatment was performed, the expense carried out in each of the strategies was assessed according to the consumed healthcare resources by each patient; the expense carried out showed important economic differences in each of the therapeutic groups. In the study, direct medical expense was quantified during the ambulatory hospitalisation for the administration of chemotherapy, of hospitalisation for surgery, and of severe toxicity. Indirect medical costs, intangible costs and fixed-asset costs (furniture, medical instruments, others) were not determined.

Costs of treatment using FEC

Healthcare was assessed in 5 major groups: diagnosis, drug application, monitoring, surgery and toxicity. See Tables 2 and 3. The group that generated greater expense was drugs for both groups of treatment with a partial total cost of $897,072.6 MXN (€69,005.58) for $4FE_{100}C$ and $1,238,169.19 MXN (€95,243.78) for $6FE_{100}C$. The rest of the costs per study group are described in Table 3.

Total cost of epirubicin was the main factor that influenced the cost by constituting 30.7% and 35.3% of total quantity for 4 $FE_{100}C$ and 6 $FE_{100}C$, respectively. Taking only into account the costs of cytostatic drugs, epirubicin constituted 95% of the expense for both therapeutic schemes and of the price list, epirubicin constituted the highest unit price; the difference was essentially the acquisition of the cost of epirubicin and less cost for the pre- and post-chemotherapy (Table 1).

On the other hand, partial total cost that corresponds to the toxicity group was generated by the salvage treatment, just increasing the number of cycles there was a risk to increase grade 3 ADR; it generated an additional expense for 6 $FE_{100}C$ of $93,675.5 MXN (€7,205.80) and for 4 $FE_{100}C$ of $7,324.4 MXN (€563.41), which caused an increase of expenses related to medical consultation, hospitalization, transfusions, antibiotics and other medications (Table 3).

Collection of patients was in different years. Once the final cost of every year was obtained, the 3% adjustment was carried out and the economic adjustments were obtained to be able to obtain the grand total cost of each therapeutic option; it was calculated in $1,780,999.57 MXN (€136,999.96) for 4 $FE_{100}C$ and $2,757,571.38 MXN (€212,120.87) for 6 $FE_{100}C$ (Table 4).

Once unit costs and the total cost of every therapeutic option were established, it was necessary to know the effectiveness (pCR); for 4 $FE_{100}C$ it was 12.5% (6 out of 48) and for 6 $FE_{100}C$ it was 20.8% (10 out of 48), Table 6 shows a difference of major effectiveness by 8.3% in favour of 6 $FE_{100}C$ against 4 $FE_{100}C$. The effectiveness probability (pCR) whilst offering 6 $FE_{100}C$ was 1.66 times (RR). The cost-effectiveness analysis was carried out by developing the following items.

Necessary cost to successfully treat one case

This is known as mean cost-effectiveness (MCE), the MCE is another form to compare the advantages or disadvantages of 4 $FE_{100}C$ against 6 $FE_{100}C$. The relative value of this intervention is expressed as

Study group	Regimen 4 FE100C (n=48)			Regimen 6 FE100C (n=48)		
	pCR n=6	pPR n=42	Partial total	pCR n=10	pPR n=38	Partial total
1. Diagnosis	16,929	132,237	149,166.00	29,442	109,474	138,916.00
2.Medications	101,936.76	795,135.84	897,072.60	255,561,32	982,607.87	1,238,169.19
3. Surgery	99,320.12	720,690.84	820,010.96	169,033.2	638,542.76	807,575.96
4. Monitoring	42,686	327,382	370,068.00	98,730	375,174	473,904.00
5. Toxicity	15.6	7,308.8	7,324.00	28,746.52	64,928.98	93,675.50
Grand Total			**$MXN** 2,243,641.96 (€ 172,587.84)			**$MXN** 2,752,240.65 (€ 211,710.81)

Complete pathological response = pCR
Partial pathological response = pPR
Costs in Mexican (MXN) pesos ($)
€= euros

Table 3: Total Cost Per groups.

Year of studyand regimen	For non/metastatic, advanced breast cancer					
	Cases (n)	$ MXN as of 2005	3% discount	Efvs	Mean C/E	Incremental C/E
4 FE100C						
2004	33	1,425,217.16	1,383,705.98			
2003	15	818,424.80	397,293.59			
Grand Total	**48**	$MXN 2,243,641.96	**$MXN 1,780,999.57** (€136,999.96)	**0.125**	**14,247,996.56** (1,095,999.68)	
6 FE100C						
2006	5	290,822.12	299,546.78			
2005	41	2,344,893.80	2,344,893.80			
2004	2	116,524.73	113,130.80			
Grand Total	**48**	**$MXN 2,752,240.65** (€211,710.81)	**$MXN 2,757,571.38** (€212,120.87)	**0.208**	**13,257,554.71** (1,019,811.87)	**11, 765,925.42** (905,071.20)

The C/E is better with 6 FE100C and the incremental C/E shows that it is necessary to pay $11, 765,925.42 MXN (€ 905,071.20) because it tells us how much it is additionally paid per each extra unit of effectiveness assuming 6 FE100C against 4 FE100C
Costs in Mexican (MXN) pesos ($); Efvs= effectiveness; C/E= cost-effectiveness, € = Euros.

Table 4: Total cost per annum, adjusted to the updating rate(3% discount).

Result	6FE100C	4 FE100C	RR	AR difference
pCR probability	10 / 48	6 / 48	20.8% /12.5%	20.8% -12.5%
	20.8%	12.5%	1.66	8.3%

RR= relative risk
AR= absolute risk

Table 5: Probability of pathologic complete response (pCR) (4 FE100C against 6 FE100C).

the quotient being obtained after dividing the total direct medical costs of $1,780,999.57 MXN (€136,999.96) with 4 FE_{100}C and of $2,757,571.38 MXN (€212,120.87) with 6 FE_{100}C amongst the effectiveness of each intervention, because it tells us how much it is additionally paid for every extra unit of effectiveness, after adding two cycles more to the treatment.

After carrying out the operations, we found that 4 FE_{100}C had a cost necessary to successfully treat a case of $14,247,996.56 MXN (€1,095,999.68) and for 6 FE_{100}C of $13,257,554.71 MXN (€1,019,811.87). The effectiveness obtained with 4 FE_{100}C was lower than with 6 FE_{100}C, then it is proved that its cost-effectiveness measured in terms of money to successfully treat a case is greater; accordingly, the highest cost of 6 FE_{100}C, in a way compensates the fact of having greater effectiveness and being more efficient (Tables 4 and 6).

Incremental cost-effectiveness ratio (ICER)

The total cost of therapeutic success of 4 FE_{100}C and 6 FE_{100}C in all 96 cases should be obtained, including the cost of the cases with toxicity secondary to chemotherapy. The ICER is obtained by dividing the difference of the cost of the intervention (numerator) amongst by the difference of the health benefit (denominator) (Table 7). The lower the ICER, it is better. When the health benefit is very low or the cost is very high, evidently the ICER will be high. The following formula is used in Table 7 to be able to obtain the ICER after comparing two therapeutic options; where Ca and Cb are the costs of the two treatments. Ea and Eb are the effectiveness of the two therapeutic arms (4 FE_{100}C and 6 FE_{100}C); ΔC is the cost increase resulting from the difference of cost of Ca vs. Cb and ΔE is the effectiveness increase resulting from the difference of effectiveness of Ea vs. Eb; values are substituted according to the formula we observe in Table 6.

The ratio between the cost increase and the effectiveness increase is denominated ICER, this means that the ICER shows that it was necessary to pay $11,765,925.42 MXN (€905,071.20) for each additional case being successfully treated which assumes 6 FE_{100}C against 4 FE_{100}C; although there is a great difference between the mean cost and the incremental cost, the latter must be carried out regardless of the expense since it is the alternative to improve the pCR rate regardless of the toxicity (Tables 6 and 7).

Univariate analysis

Our calculations of univariate sensitivity analysis reinforce the robustness of the results, after adjusting the 3% discount rate only from the direct medical costs. The strategy with 6 FE_{100}C had greater effectiveness despite the highest cost in front of the 4 FE_{100}C scheme. In terms of dominance, the likelihood to offer 4 FE_{100}C is strictly dominated by 6 FE_{100}C.

Discussion

This study compared two therapeutic options to treat the advanced breast cancer by considering the effectiveness, toxicity and the number of cycles without modifying the intensified dose of epirubicin to show advantages and disadvantages from the pharmacoeconomic point of view.

Not only does the adequate handling of the disease require the availability of physicians, early and timely diagnosis and an ample infrastructure of medications available in a SSP with insured population (IMSS), but also economic evaluations helping in the decision making, above all, what medications are the most indicated in every case.

Given that there is no reference pattern related to the CEA of the neoadjuvant chemotherapy (with FE_{100}C) in the treatment of advanced breast cancer, the information was supported with CEA studies of adjuvant chemotherapy with epirubicin to treat early breast cancer, by showing the efficacy of epirubicin in terms of cost-effectiveness [18,19].

From the clinical view, randomised and review studies have shown the usefulness of anthracyclines (epirubicin, doxorubicin) as first line in NCT, where the 3-to-4-cycle chemotherapy schemes have reported a very variable rate of pCR of 3% - 14% [10,14,31-35]; however, it was decided to use schemes with 6-cycle anthracyclines, since they have improved the pCR rate between 15% and 24% [9,36-42].

The fact of increasing the number of cycles of 4 to 6 with FE_{100}C generated an increase of expense percentage, after only comparing the

Values are substituted in the following formula:
• ICER= Ca – CbΔC ---------- =------= Ea – EbΔE
$2,757,571.38 - $1,780,999.57976,571.81 • ICER= (€ 212,120.87 - € 136,999.96)(75,120.91) ---------- = ---------- = .208 - .125 .083
• ICER= $MXN 11,765,925.42 (€ 905,071.20)

C= cost, E= effectiveness, _C= cost increase, _E= effectiveness increase.

Table 6: CEA of 4 FE100C against 6 FE100C. Formula to obtain the incremental cost-effectiveness ratio (ICER).

Options	C	E	MCE	ΔC	ΔE	ICE
4 FE100C	$1,780,999.57 MXN (€136,999.96)	0.125	14,247,996.56 (1,095,999.68)			
6FE100C	$2,757,571.38 MXN (€212,120.87)	0.208	13,257,554.71 (1,019,811.87)	976,571.81 (75,120.91)	0.083	11, 765,925.42 (905,071.20)

C= cost, E= effectiveness, MCE= mean cost-effectiveness, ICE= incremental cost-effectiveness, _C=
cost increase, _E= effectiveness increase.

Table 7: CEA: Costs and results of two options for treating the same disease (4 FE100C against 6 FE100C).

cytostatic drugs, it was only 33.7% and the total cost 35.4%, this makes it discussable to set it out as standardized treatment in our hospital compared against other drugs with indication in the LABC treatment; thus, we consider to carry out a CEA as necessary.

From the CEA study regarding the treatment, by only increasing the number of cycles, it generated a higher cost of drugs, but from the clinical point of view, the gastric and hematological toxicity rate, overall, was similar in both treatments; the dose increase of epirubicin 100 mg/m^2 in the 6 FEC scheme was well tolerated, the main toxicity was vomiting (52.4%), nausea (91.6%) and alopecia (100%), and developed low incidence of severe neutropenia (2.4%) and moderate anemia (2.08%) without having an effect in the LABC prognosis. There were no adverse effects in cardiac function.

In the CEA study, moderate anaemia generated by the treatment with 6 FE_{100}C was the one that generated the greatest consumption of costs in the toxicity group due to the supplies for blood transfusion and hospitalization, despite the increase of medical direct cost; the treatment still had cost-effectiveness.

Results must be interpreted within the context which this study has developed, with its limitations, such as the small size of the sample, the absence of evaluation of the quality of life, the exclusion of the analysis of indirect costs linked with invalidity of surviving patients; despite this, including these costs is uncommon in many pharmacoeconomic studies [18,19,43,44].

It is established that the 6 FE_{100}C scheme had greater effectiveness with an 8.3% difference regarding 4 FE_{100}C and slightly more expensive by 18% after comparing it against the total cost with 4 FE_{100}C, where epirubicin was the greatest contributor for the costing of treatment.

In spite of the limitations of this CEA study, the obtained results are relative and they may not be extrapolated to other studies since there are no comparisons, but results can be obtained yet being partial from the costs of cytostatic drugs, since these costs can be perfectly reproducible in every oncological center, in fact, every cytostatic drug is the main medication responsible for the cost increase of the oncological treatment [45,46].

Study results have robustness according to the univariate sensitivity analysis and despite the cost increase with 6 FE_{100}C, this therapeutic method continues to be a more economical option in spite of the introduction of new therapies, such as taxanes, gemcitabine and capecitabine [47-50]. Results obtained show the fact that the use of regimen with 6 FE_{100}C is the therapeutic alternative that allows achieving a benefit in the effectiveness despite having a higher cost; the ICER establishes a necessary cost of $11,765,925.42 MXN (€905,071.20) for each additional case being successfully treated assuming 6 FE_{100}C against 4 FE_{100}C, this would allow performing a greater percentage of surgeries with healing character; if we dealt with patients with metastatic breast cancer, an ICER analysis would be much more elevated due to the fact that differences in effectiveness are smaller. In addition, if a limited or fixed budget is taken into account, fewer ill people can be treated and less lives saved with 4 FE_{100}C.

Quality of Life

Some studies have assessed the quality of life (QoL) by integrating adapted questionnaires (EORTC QLO C-30) before and after chemotherapy with FEC, QoL initially decreases in all schemes during treatment, but QoL improves later by comparing against non-treated patients [51-54].

Based upon these important studies that value QoL, an important difference was not detected that affected the QoL, amongst the number of cycles given in our study (4 vs. 6) thus, a cost-usefulness study was not set out defining the quality-adjusted life-year (QALY).

Conclusion

Depending upon the method chosen, the increase of spent money is mainly influenced by the increase in the unit price of cytostatic drugs, the number of cycles given and the inflation factor.

The most appropriate therapeutic option for patients with advanced and metastatic breast cancer must be based with the extent of certainty that offers a treatment after producing a benefit according to the quality of the study which justifies its use and the amount of benefit obtained after measuring in efficacy and effectiveness. The results confirm the high cost of LABC medical care in an SSP.

The 6 FE_{100}C scheme is the strategy with better and more efficient short-term incremental cost-effectiveness to treat LABC, the increase in the number of cycles and epirubicin 100 mg/m^2 dose were well tolerated, without increase of overall severe toxicity; the calculations indicate that it is possible to establish the 6 FE_{100}C scheme as neoadjuvant treatment in our hospital and, on the other hand, it would be benefited in scenarios where resources are limited.

Despite the information, NCT options are still required with new drugs that both improve the survival in a greater number of patients and have important economic implications affecting the health benefit.

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