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## Costs of breast cancer treatment prior to the introduction of immune-based therapy in México

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### Resumen

**Introducción:** análisis de costos sobre datos directos del manejo integral provisto a mujeres con cáncer de mama antes de la introducción de inmunoterapia en el Instituto Nacional de Cancerología.

**Métodos:** se realizaron cálculos de costos directos sobre datos individuales en un subgrupo de 309 pacientes seleccionadas al azar, para extrapolarlos a 633 pacientes tratadas durante 2004. Se obtuvo información sobre la utilización de recursos por cada paso de la atención. Los costos se expresan en dólares norteamericanos (USD) al 2008, ajustados a una tasa de inflación de 3 % anual.

**Resultados:** 41, 191, 240 y 58 pacientes correspondieron a los estadios clínicos I a IV, con 103 pacientes referidas de otras instituciones sin estadificación. El costo anual del manejo por cada paciente con cáncer de mama en estadio I fue de 6219.94 USD; en estadio II, 7498.04 USD; en estadio III, 9610.31 USD; en estadio IV, 9917.82 USD; y sin estadificación, 7504.41 USD. El costo exacto integral total fue de 5 341 805.37 USD.

**Conclusiones:** antes de la introducción de inmunoterapia, los costos integrales del cuidado de mexicanas con cáncer de mama aumentaba al avanzar la enfermedad, en parte por una proporción significativa de pacientes diagnosticada tardíamente.

### Palabras clave

neoplasias de la mama  
costos y analisis de costos  
economía farmacéutica  
trastuzumab

### Summary

**Background:** the aim was to perform a cost analysis on direct data of integral medical care provided to BC patients prior to introduction of immunotherapy.

**Methods:** a total of 633 patients were studied. Direct costs calculations were performed on individual patient data in a subset of 309 randomly selected patients, extrapolating calculations to the universe of 633 patients. Information was obtained for each management process (diagnosis and staging, cancer management, symptoms control, palliative care and follow-up). Costs are expressed in 2008 US dollars (USD) and adjusted to a 3 % discount rate.

**Results:** the clinical stage distribution in the 633 patients was 41, 191, 240 and 58 patients for clinical stages I to IV, respectively; with 103 patients referred from other institutions without staging. The annual costs of care per patient was, in clinical stage I: 6,219.94 USD; stage II: 7,498.04 USD; stage III: 9,610.31 USD; stage IV: 9,917.82 USD; and in patients without staging: 7,504.41 USD. The exact total integral cost according to the universe of BC patients ( $n = 633$ ) by 2004 was 5,341,805.37 USD.

**Conclusions:** before the introduction of immune-based therapy costs of care for Mexican women with BC increased with advanced stages do to a significant proportion of patients were diagnosed late.

### Key words

breast neoplasms  
costs and cost analysis  
economics, pharmaceutical  
trastuzumab

Breast cancer (BC) is the most frequent neoplasm among women worldwide. In the year 2002, it was estimated that 636,000 new cases occurred in developed nations and 514,000 were diagnosed in low-income countries.<sup>1</sup> During the 2002-2007 period, the number of new cases of BC in developing nations doubled (15 %) that of developed countries (7 %).<sup>2</sup> Mexico is showing an important increase in the number of BC cases, with 9,490

new diagnoses which were reported in 1998, and 12,433 by the year 2003.<sup>3</sup> Developed countries are tackling the problem with timely detection programs and the use of more specific drugs, such as the employment of immune-based therapy. These strategies are achieving a sensible reduction in mortality. However, this scenario is quite different in poor countries, where a high percentage of cases are diagnosed at advanced clinical stages.<sup>4-6</sup>

The choice of a therapeutic strategy requires careful clinical evaluation aimed to define a cost-effective modality that is proper at the individual patient level.<sup>7</sup> Thus, an adequate strategy would provide the best of current clinical care, while avoiding unnecessary costs and concerns to patients, their families and institutions. At the National Institute of Cancerology (INCan), Mexico, we carried out a complete medical costs of care study in patients treated at the BC Service, prior to the introduction of immune-based therapy, which included all clinical stages, different therapeutic alternatives and response rates.

## Methods

For this retrospective descriptive analysis we estimated prevalent costs on individual patient data in a fixed calendar year (the fiscal year 2004).<sup>8</sup> We included all clinical files of the period comprising January 1 to December 31, 2004, prior to the introduction of therapeutic monoclonal antibodies. A total of 633 clinical files of patients treated at the INCan BC Service were reviewed. Distribution by clinical stage was as follows: 41 patients for clinical stage I; 191 for stage II; 240 for stage III; 58 patients for clinical stage IV, and 103 patients who were surgically managed in other institutions and later referred to our service. For the analyses of costs, the sample size was estimated according to the size of the population registered during 2004, with a 95 % confidence interval (CI), a 5 % margin of error, and assuming a 50 % maximal variance [ $Sy^2 = p(1-p)$ ]. Selection of the sample was performed randomly by using electronic table numbers. Sample size was determined with the following calculations:

Sample estimate

$$x = Z(A/100) 2r(100-r)$$

Sample size

$$n = Nx / [(N-1) E^2 + x]$$

Margin error

$$E = v [(N-n) x/n (N-1)]$$

Where:

N = population size

n = sample size

R = fraction of response of interest

A = confidence level Z ( $\alpha/100$ ): Critical value for confidence level  $\alpha$ .

Total resources utilization registry was obtained from review of each patient's file, calculated in 2008 adjusted Mexican pesos with a 3 % discount rate. We performed integration of

direct medical costs, from the institutional viewpoint, categorized in three phases: 1) Diagnostic and staging costs. 2) Treatment phase costs, and 3) the costs of patient follow-up with palliative support (if applicable) and medical backing. Resources use was measured for each of the variables for which costs were calculated. Thus, the diagnostic and staging phase included a first medical evaluation, first appointment, biopsy and/or X-ray exams, immunohistochemical analyses, laboratory and office studies, risk cardiovascular evaluation, and an appointments with specialists. In the treatment phase, we evaluated the type of surgical intervention, cost of radiotherapy (Rt), as well as first-, second-, third-, and fourth-line chemotherapy (Ct), paramedical care services and the costs of non-oncological drugs prescribed for management of complications or for side effects prevention. Within the follow-up and medical support phase, we considered subsequent consultations for different surgical, Rt, medical oncology, laboratory and office tests, as well as treatment of complications.

The costs of all procedures for the fiscal year 2008 were provided by the INCan Accounting Department. For the presentation of data, costs are expressed in American dollars (USD) year 2008, and the costs of drugs and goods was obtained from those published at the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS) web site: <http://200.34.143.57:8080/wijsp/PDFIMSS/IMSSComproBienesTerapeuticosNLO.pdf>. In addition, we analyzed age of patients, surgery type, socioeconomic level (determined at the INCan, according to income, expenses, type of employment, and number of economic dependents). This classification included six levels. According to INCan regulations, for cases classified as level 1, the patient pays 5 % of medical services and the institution pays 95 %, while for patients classified at level 6, the patient pays 75 % and the institution 25 %. In all cases, the patients absorbed the costs of drugs. The patients' health status at the last hospital consultation was also considered in the present analyses. We performed a descriptive analysis with central tendency and dispersion measures with parametric and non-parametric statistics according to data behavior and simple and accumulated frequencies, as well as statistical analysis of the variables of resources utilization and costs, lost-data analysis, and also analysis of censored-data costs.<sup>9</sup>

## Results

The distribution of clinical stages in the total 633 patients treated in our institution in 2004 was 41, 191, 240 and 58 for clinical stages I to IV, respectively; and 103 patients referred from other institutions without staging. The study sample ( $n = 309$ ) was distributed across BC clinical stages as follows: 24 patients for stage I, 88 for stage II, 104 for stage III, 33 for stage IV, and 60 patients without staging because they previously underwent surgery or received incomplete oncological treat-

ment before presentation to our institution. Mean age of the study sample was 51.24 years (range: 43.6-58.8 years). A total of 85 % of tumors were infiltrating adenocarcinomas. Socioeconomic status was classified according to the six levels standardized by the INCan for each patient. In all, 6.63 % of patients were classified as socioeconomic level 1, 38.91 % as level 2, 37.02 % as level 3, 12.66 % as level 4, and 0.89 % of patients as socioeconomic level 6.

### Costs analysis

The average treatment duration was 9.6 months for the universe of 633 patients. Among 41 patients at clinical stage I, 15 (36.36 %) patients were treated with surgery, the cost of which represented 2,834.87 USD; 5 (13.64 %) patients received Ct plus Rt, with total cost of 1,031.56 USD. Patients who received Ct plus Rt followed by surgery represented 36.36 % of patients at clinical stage I, with a total cost of 5,102.94 USD; and six of the 41 patients at stage I received Ct plus surgery, for a total cost of 3,575.46 USD. For this same group of patients, those who received first-line Ct based on cyclophosphamide + doxorubicin + fluorouracil (FAC

regimen) comprised 75 % of patients; paclitaxel + cisplatin (CDDP) + gemcitabine comprised 16.67 %; and 8.33 % of the patients received doxorubicin + cyclophosphamide. A total of 28.57 % of patients in clinical stage I received a second line Ct, 50 % were based on CDDP + gemcitabine + doxorubicin + Rt, and the remaining based on FAC + gemcitabine. For the group of 41 patients at stage I, the costs of follow-up consultations and hormonotherapy were summed up, with a global cost increase of 983.87 USD per patient-years. Total costs of diagnostic work-up, staging, treatment and follow-up visits for clinical stages II–IV are shown in tables I to III. Of the patients in clinical stage I, 48 % received hormonotherapy, 92 % of these patients with tamoxifen. Of patients at stage II, 32.25 % of patients received hormonotherapy (84 % with tamoxifen); of patients at stage III, 51.92 % received hormonotherapy (84 % tamoxifen), and for patients at stage IV, 51.52 % received hormonotherapy (72 % tamoxifen).

Costs of care per patient according to clinical stage, taking into account the diagnostic phase, treatment, and follow-up visits, was as follows: for patients in clinical stage I: 6,219.94 USD, patients in stage II, 7,498.04 USD, patients in stage III 9,610.31 USD, patients in stage IV 9,917.82 USD, and for patients who

**Table I** | Costs of care of breast cancer patients at clinical stage II, INCan, Mexico (n = 191)

Alternative	%	Cost (95 % confidence interval) USD*
Diagnosis	5.4	889.60 (837.65-941.56)
Surgery	16.4	2 695.75 (2 395.72-2 995.89)
Chemotherapy + radiotherapy	28.1	4 608.23 (3 810.73-5 404.23)
Chemotherapy + radiotherapy + surgery	31.5	5 168.59 (3 730.76-6 063.18)
Radiotherapy + surgery	18.6	3047.29 (2 546.54-5 479.49)
Hormonotherapy + support services		366.57 (241.35-491.81)
Medical follow-up visits		510.16 (435.83-584.48)

\*American dollars

**Table II** | Costs of care of breast cancer patients at clinical stage III, INCan, Mexico (n = 240)

Alternative	%	Cost (95% confidence interval) USD*
Diagnosis	3.0	876.29 (830.19-922.32)
Other treatments	9.3	2 694.98 (2 394.97-2 994.87)
Surgery + chemotherapy	22.6	6 572.71 (6 543.18-6 598.43)
Chemotherapy + radiotherapy + surgery	28.7	8 354.35 (7 755.29-8 955.07)
Chemotherapy + surgery	16.5	4 808.22 (3304.15-6 312.52)
Chemotherapy + radiotherapy	10.5	3 048.75 (2 547.67-3 549.59)
Surgery	9.4	2 721.79 (2 577.71-2 872.95)
Hormonotherapy + support services		USD \$339.22 (191.44-487.08)
Medical follow-up visits		USD \$705.29 (612.17-798.13)

\*American dollars

received a surgical intervention in other institutions, the total cost per patient was 7,504.41 USD. The global cost for each clinical stage and according to the universe of patients treated at the INCan was 5,341,805.37 USD (table IV). Near 89 % of the total expenses was exercised during the first year of treatment, over a mean treatment length of 26 months.

Clinical status of the 633 BC patients for whom extrapolation of costs analyses were applied, at an average of 23.6 months of follow-up in clinical stages I-IV, was as follows: in clinical stage I, 32 (79.17 %) patients were alive without tumor activity (TA), and two (4.17 %) patients presented TA; the status was unknown for seven patients (16.16 %). At stage II, 145 (76.14 %) patients were alive without TA, 26 (13.64 %) patients were alive with TA, and 20 (10.22 %) patients were lost to follow-up. In clinical stage III, 152 (63.46 %) patients were alive without TA, 44 (18.27 %) patients were alive with TA, 14 (5.78 %) patients died, and the status was unknown for 309 (12.49 %) patients. In stage IV, 10 (18.18 %) patients were found without TA, 23 (39.39 %) patients died as a direct consequence of BC, seven (12.12 %) patients died for other causes, and 18 (30.31 %) patients were lost to follow-up (figure 1).

## Discussion

BC mortality is greater in low-income countries than in developed nations.<sup>2,4</sup> To a great extent, this is due to a limited access to a timely diagnosis and personalized therapies.<sup>5,6,10</sup> In this study, we analyzed the costs of all interventions performed for all the different clinical stages of Mexican women with BC. The INCan is a third-level public, national referral institution that provides care mainly to low-income persons. In the present report, 82.6 % of patients were classified in socioeconomic levels 1-3; which means that our institution absorbs about 85 % of the costs generated for medical care, excepting the costs of drugs. Also, we observed that most BC patients (68.1 %) sought medical care at relatively advanced stages (II and III), contrasting with developed countries, in which care for early clinical stages predominates (i.e., 61 % at stage I).<sup>7,11</sup> Consequently, costs of care in advanced stages are higher at almost all different intervention phases, principally during treatment and follow-up phases. This picture has also been observed in low-income women from USD,<sup>7</sup> but this information is lacking for developing nations.

**Table III** | Costs of care of breast cancer patients at clinical stage IV, INCan, Mexico (n = 58)

Alternative	%	Cost (95 % confidence interval)	
		USD*	
Diagnosis	3.6	878.11 (760.88-995.43)	
Radiotherapy	4.5	1 100.85 (834.05-1 367.53)	
Chemotherapy	16.9	4 094.78 (3 091.75-5 097.03)	
Chemotherapy + radiotherapy	30.7	7 439.01 (5 966.20-8 910.06)	
Chemotherapy + radiotherapy + surgery	44.2	10 693.40 (8019.19-13 365.52)	
Hormonotherapy + support services		554.44 (214.54-894.42)	
Medical follow-up visits		894.42 (671.75-1 022.52)	

\*American dollars

**Table IV** | Institutional expenses for patients with breast cancer, INCan, Mexico

Clinical stage	Population treated in 2004	Total cost per patient in USD*	Total institutional costs per clinical stage in USD*
I	41	6 219.94	255 017.54
II	191	7 498.04	1 432 125.64
III	240	9 610.31	2 306 474.40
IV	58	9 917.82	575 233.56
V	103	7 504.41	772 954.23
		Total	5 341 805.37

\*American dollars

Approximately 70 % of women with BC have tumors that express hormonal receptors, a characteristic associated with a more favorable outcome after endocrine-based therapy, as compared with women with tumors negative to steroidal receptors.<sup>12,13</sup> Another molecular marker of prognostic importance is the human epidermal growth factor receptor 2 (HER-2), which is overexpressed in 20 % of breast carcinomas.<sup>14,15</sup> Overexpression of this receptor confers a more aggressive biological behavior with high recurrence rate, metastasis, and lower global survival.<sup>13-15</sup> A humanized monoclonal antibody directed against HER-2 protein, i.e., trastuzumab, has demonstrated inhibition of tumor growth, when administered alone or in combination with other antineoplastic agents for HER-2-positive tumors.<sup>16-19</sup> This immune-based therapy has shown an improvement in disease-free survival and pathological response,<sup>16,17</sup> and it has proved to be cost-effective in developed countries.<sup>18</sup> However, there is a notorious increase in costs of care with immunebased therapy. Confronted by this scenario, clinics, institutional administrators and policy makers of low-income countries urge to conduct economic evaluations of the current use of treatments with and without monoclonal antibodies.<sup>10</sup> Hence, the present report provides relevant clinical information that may help in designing better public health policies in low-income countries. Moreover, this study established the basis for future comparisons of new treatment strategies in terms of cost-utility.

In our patients, we observed that the average cost during the diagnostic phase was near 1,000 USD. Differences in costs depend strongly on the patient's clinical stage at first medical encounter. Noteworthy, the highest expense is found in patients who received treatment in a previous institution and who needed more extensive revision of histopathology blocks, immunohistochemistry and imaging studies for precise determination of disease extension. In the treatment phase, which comprises

surgery, chemotherapy schemes, radiotherapy, hormonotherapy, drugs for symptoms control and antimicrobials, the total expenses averaged 6,500 USD. It is evident that at a more advanced clinical stage, our patients required higher resources to evaluate disease extent, to initiate chemotherapy management, to treat recurrences and metastases and to improve quality of life.<sup>19</sup> During the follow-up phase, the expenses in medical care services, consultations, laboratory assays and hormonotherapy also averaged 1,000 USD per patient, also higher at advanced stages. We observed that costs increase with advanced disease stages, when therapeutic response diminishes. This negative association between expenses and effectiveness has been previously observed in Mexico by Knaul et al. in a study of patients treated for BC from 2002 to 2006 at the Mexican Institute of Medical Security (IMSS).<sup>20</sup> Similarly, we observed 16 % patients who were lost to follow-up, for whom disease evolution and annual expenses calculation could not be performed accurately.

In conclusion, cost of care of patients treated for BC increases with advanced stages, when therapeutic response usually diminishes. Our report provides information derived directly of institutional records that may establish the basis for the rational use of resources in a developing country. In the near future, new studies will evaluate the cost-utility relationship of newer drugs and diagnostic techniques, and will compare the scenario with that presented here.

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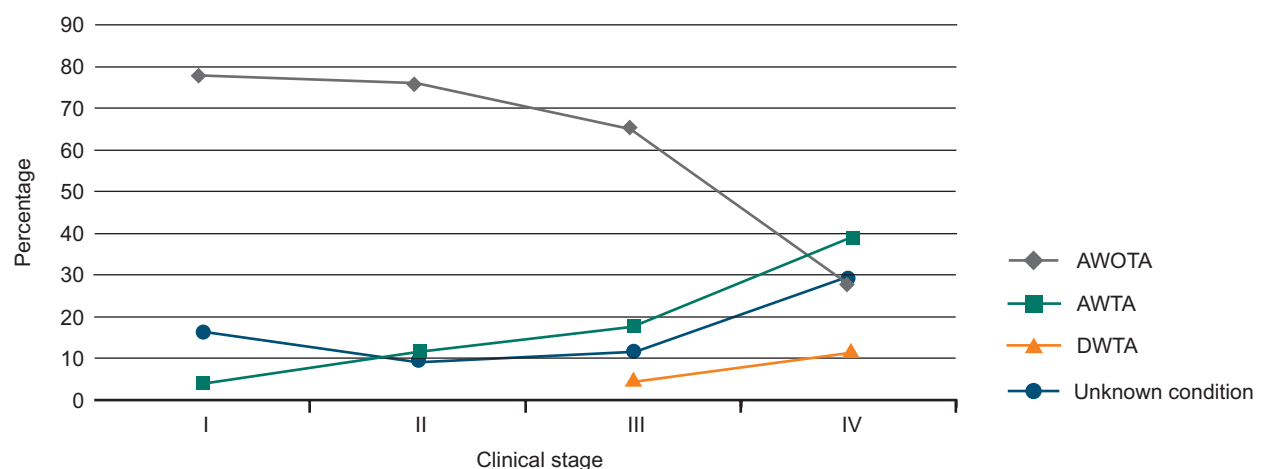


Figure 1 | Breast cancer clinical stage of patients at their last consultation. AWOTA = alive without tumor activity, AWTA = alive with tumor activity, DWTA = died with tumor activity

pharmaceutical companies did not participate, either directly or indirectly in study design, random selection of patients, data capture, data analysis, manuscript draft or the decision to submit for publication.

## Disclosure declaration

Dr. Chiquete-Anaya reports receiving consulting fees, and lecture (including speakers and writers murean) fees from Sanofi: No other potential conflict of interest relevant to this article was reported.

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