COST-EFFECTIVENESS OF ANASTROZOLE, IN COMPARISON WITH TAMOXIFEN, IN THE ADJUVANT TREATMENT OF EARLY BREAST CANCER IN BRAZIL

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SUMMARY

OBJECTIVE. Breast cancer, a leading type of cancer in many developing countries, is the most frequent non-cutaneous tumor in Brazil. Hormone therapy is the standard of care in the adjuvant treatment of early-stage, hormone-receptor-positive disease, and both tamoxifen and third-generation aromatase inhibitors are options in postmenopausal women. The comparative cost-effectiveness of different treatment strategies is of considerable interest in societies facing limited resources.

METHODS. In an attempt to compare cost-effectiveness of upfront treatment with tamoxifen or anastrozole, the medical and economic results in a hypothetical cohort of 64-year-old postmenopausal women, was analyzed considering the Brazilian healthcare system in 2005, the primary perspective of the private sector, and a lifetime horizon. Data from the ATAC Trial, Markov modeling, a modified Delphi panel, and microcosting (in Brazilian R$) were used to estimate costs and effectiveness of the two upfront strategies.

RESULTS. The model estimated a gain of 0.55 discounted life-years for patients receiving anastrozole, relative to those treated with tamoxifen. With an incremental cost of R$ 15,141.15, the model estimated that the cost-effectiveness of anastrozole, in relation to tamoxifen, was R$ 27,326.80. Monte Carlo simulations showed that approximately 50% of the cases fell below the threshold of R$ 29,229.00 per life-year gained, which is recommended by the World Health Organization for Brazil.

CONCLUSION. It was concluded that upfront anastrozole is a cost-effective option compared with tamoxifen in the adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer.

new primary breast cancer or death from any cause produced by anastrozole, compared with tamoxifen, was 17% in patients with hormone-receptor-positive tumors; in this same group, the relative risk reduction of recurrence or of a new primary breast cancer was 26%11.

Given the superiority of upfront treatment with an aromatase inhibitor, compared with tamoxifen10,11, cost-effectiveness of these two agents is of interest especially in societies with limited resources. In this study, we sought to determine cost-effectiveness of anastrozole, compared with tamoxifen, in the adjuvant treatment of postmenopausal women with early breast cancer in Brazil. In addition, measurements in terms of life-years gained with the use of anastrozole, were also carried out.

METHODS
Development of the model
We used a hypothetical cohort of 64-year-old postmenopausal women undergoing definitive surgery for local treatment of early breast cancer. These hypothetical patients were assumed to be similar to those from the ATAC trial. The study setting is the Brazilian healthcare system in the year 2005, with the primary perspective of the private healthcare sector (insurance companies, healthcare plans, health maintenance organizations and healthcare cooperatives), and with the lifetime horizon considered. We obtained data from the medical literature, including the ATAC trial10,11, the official published prices for medications13, procedures14, and hospital supplies15 in Brazil, and national population statistics16. Information on the local patterns of care for breast cancer, complications and costs were obtained using a modified Delphi panel, a method commonly used in pharmacoeconomic studies17.

A Markov model was developed reflecting the natural history of breast cancer after a potentially curative local surgery. Markov models are used to represent the possible transitions of patients from one discrete health state to another in one of a finite number of states. Such models are useful when risks are continuous over time, when the timing of events is important, and when events may occur more than once. The health states used in the model were (1) alive and well, (2) locoregional or (3) distant recurrence, (4) experience of adverse event due to adjuvant treatment; (5) need to change treatment after an adverse event, (6) death from breast cancer, and (7) death from other causes. The model was used to simulate two cohorts of patients starting adjuvant treatment, one receiving anastrozole (1 mg per day for the planned 5 years), and the other receiving tamoxifen (20 mg per day for the planned 5 years). In order to compensate for the uncertainty of the model parameters, we performed ten thousand Monte Carlo interactions, with variations in all the parameters.

Health States and Costs
The model assumed that all patients will receive adjuvant treatment (anastrozole or tamoxifen), and that each year the patients will transit among the health states previously described. Patients began in the health state “alive and well”. The model considered the possible transitions from this state to those involving recurrence and death from other causes, with contralateral breast cancer considered as locoregional recurrence. The model assumed that after locoregional or distant recurrences, no patient would return to the "alive and well" state, given that some studies suggest that patient outcome is not affected by local salvage treatment18, and that only a minority of patients with local recurrence after mastectomy19 or conservative surgery20 have a prolonged survival. Patients who died during the simulation did not make further transitions.

Microcosting was used to evaluate use of resources and cost of distinct clinical states (Table 1). Costs were calculated in Brazilian Reais (R$, with R$ 1.00 equaling approximately US$0.40) using a discount rate of 3%, and performing sensitivity analyses for the economic results varying discount rates from 1.5% to 5%, given the inherent uncertainty of the clinical and economic data. Incremental cost-effectiveness ratios are reported for the lifetime horizon.

Probabilities
Probabilities of adverse events were those observed in the ATAC trial11. Probabilities of recurrence derived from the time-to-recurrence curve of the ATAC trial, with a 26% reduction in women with hormone-receptor-positive tumors using anastrozole, compared with tamoxifen11. The model attributed probabilities of locoregional and distant recurrences in each group using data from the ATAC trial, assuming a constant pattern along the simulation. Such probabilities were 34.16% and 65.83% for locoregional and distant recurrences, respectively, in the anastrozole group, and 40.11% and 59.89% for locoregional and distant recurrences, respectively, in the tamoxifen group15. Outcome was simulated in terms of recurrence after the original trial follow-up period, assuming that the benefit of adjuvant anastrozole would last for the entire life of the patient. To achieve such a goal, an exponential function adjusted to extrapolate the original curve, as shown in Figure 1, was used.

After recurrence, the probability of death was influenced by the initial disease-free interval18,19,21,22. As early recurrence typically portends a worse prognosis, the annual probabilities of distant disease and death in the model were greater in the first five years, in comparison with subsequent years. For death from breast cancer, annual probabilities were 0.50 in the first year, 0.41 in the second, 0.32 in the third, fourth and fifth, and 0.22 from the sixth year onwards23. The annual probabilities of distant disease after local recurrence derived from the curve presented by Kamby and Sengelov24. Finally, the annual probability of death from other causes was obtained from Brazilian vital statistics of 200116.

<table>
<thead>
<tr>
<th>Health state</th>
<th>Costs (R$)</th>
<th>Anastrozole</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive and well from years 1 to 5</td>
<td>1,255.87</td>
<td>1,339.57</td>
<td></td>
</tr>
<tr>
<td>Alive and well 6 years onwards</td>
<td>551.64</td>
<td>635.34</td>
<td></td>
</tr>
<tr>
<td>Treatment suspension from years 1 to 5</td>
<td>1,255.87</td>
<td>1,339.57</td>
<td></td>
</tr>
<tr>
<td>Treatment suspension 6 years onwards</td>
<td>551.64</td>
<td>635.34</td>
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<tr>
<td>Adverse event</td>
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<td>966.3</td>
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<td>Locoregional disease</td>
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<tr>
<td>Metastasis</td>
<td>14,639.04</td>
<td>14,639.04</td>
<td></td>
</tr>
<tr>
<td>Death due to breast cancer</td>
<td>6,131.40</td>
<td>6,131.40</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS

Effectiveness
Considering a lifetime horizon, the adjuvant treatment with tamoxifen resulted in 14.39 discounted life-years gained. With use of anastrozole, there was an additional gain of 0.55 discounted life-years, resulting in 14.94 discounted life-years gained. The discount rate used for the consequences was 1.5%.

Costs
The mean lifetime cost, discounted at 3%, was R$ 47,565.45 for a patient receiving anastrozole, and R$ 32,424.30 for one receiving tamoxifen. For patients receiving anastrozole, approximately 49% of the cost was due to the drug itself. On the other hand, for patients receiving tamoxifen, nearly 46% of the expenses were for treatment of recurrences. The model predicts that such patients expend 17% more in recurrence treatment, when compared to patients receiving anastrozole. However, patients receiving anastrozole are predicted to expend, on the average, 15% more resources with post-treatment disease remission, in comparison with those receiving tamoxifen.

Costs related to the health states “locoregional recurrence”, “distant recurrence” and “death” are higher in the group of patients treated with tamoxifen, whereas the cost during the “alive and well” state is higher for anastrozole.

Cost-effectiveness
During simulation involving the lifetime horizon, considering the gain of 0.55 discounted life-years for patients receiving anastrozole in relation to those receiving tamoxifen, and with an incremental cost of R$ 15,141.15, the model estimated that cost-effectiveness of anastrozole, in relation to tamoxifen, was R$ 27,326.80 (Table 2). Several univariate sensitivity analyses were performed (data not shown). The model was sensitive to the cost of adjuvant therapy and to probability of interrupting adjuvant treatment with anastrozole. Regarding tamoxifen, the model was sensitive to the cost of metastatic disease, probability of metastasis and probability of interrupting adjuvant treatment with tamoxifen. Figure 2 depicts findings of ten thousand Monte Carlo simulations for cost-effectiveness results. The line shows the threshold of R$ 29,229.00 per life-year gained, with approximately 50% of the simulations being below this threshold.

DISCUSSION
Performance of a decision analytical model considering the Brazilian setting is indeed necessary because healthcare decision makers, mainly budget holders, must make decisions regarding reimbursement and inclusion of given drugs or interventions in therapeutic settings. A decision analytical model considering the Brazilian scenario is also needed because transferability of cost-effectiveness results from other countries is still a matter of research, can be potentially misleading and result in inefficient use of the scarce healthcare resources. Clinical data, on the other hand, are likely to be, for the most part, consistent between populations of different countries, and therefore clinical results can largely be extrapolated across national borders. In fact, in this model it was assumed that Brazilian women with early breast cancer are similar to those studied in the ATAC trial. Once again, current evidence suggests that treatment effect and relative risk reduction may be more generalizable than prices, clinical practice patterns and resource use. As a matter of fact, approaches that have been used for transferability advise that, at a minimum, there is a need for country-specific substitution of practice pattern data as well as unit cost data. In order to identify the Brazilian clinical practice patterns and resource usage a modified Delphi study is needed.
panel was performed with Brazilian specialists, and results were used in the microcosting process. In view of the latest ATAC results, it can be stated that up to the 108th month this model was able to adequately predict the pattern of disease free survival in this simulated population. This can be observed comparing the absolute percentual difference between tamoxifen and anastrozole patients who have recurrent disease at the 108th month in the ATAC trial and in this model: 4.1%27 and 4.0%, respectively. Further, the uncertainty surrounding clinical and economic data was assessed in this study by means of probabilistic sensitivity analysis (Monte Carlo simulation).

In many developed countries, acceptable cost-effectiveness thresholds have been defined for planning healthcare policies. However, no such definition is available in Brazil, a developing country facing limited healthcare resources. The World Health Organization (WHO) has suggested an acceptable cost-effectiveness threshold as one that is less than three times the per-capita gross domestic product (GDP). In Brazil, where the yearly per-capita GDP is currently R$9,743.00, an intervention with a cost-effectiveness of up to R$29,229.00 may therefore be considered as cost-effective by WHO standards. This model estimated that the lifetime cost-effectiveness of adjuvant treatment with anastrozole, in comparison with tamoxifen, is R$27,326.80, when considering a 64-year-old postmenopausal patient with hormone-receptor-positive, early breast cancer.

Several other cost-effectiveness models for the comparison between adjuvant treatment with anastrozole or tamoxifen have been published. Hilnner conducted a computer simulation model assessing the outcomes of 64-year-old women with estrogen-receptor-positive breast cancer treated with adjuvant anastrozole or tamoxifen for 5 years, using data from the ATAC trial. His model predicted that adjuvant anastrozole would result in improvements in disease-free survival of 2.9 and 5.3 months after 12 and 20 years, respectively. In terms of overall survival, such improvements would be 0.9 months and 2.0 months, respectively, resulting in incremental cost-effectiveness lower than R$100,000 per life-year after 12 years. In addition, inclusion of quality-of-life weightings for nonfatal outcomes modestly favored anastrozole in the short term; in the long term, however, an increased risk of hip fracture from the use of anastrozole would curtail such benefit. They concluded that, from the societal perspective, the average woman will experience an overall lifetime benefit from the adjuvant use of anastrozole, with the incremental cost of this benefit near the upper limit of the range of incremental costs arbitrarily accepted in North America. A second analysis conducted in the United States, on behalf of the ATAC Trialists’ Group, concluded that upfront anastrozole is a cost-effective alternative to tamoxifen for the adjuvant treatment of postmenopausal women with estrogen-receptor-positive, early breast cancer.

Rocchi and Verma conducted an economic analysis comparing anastrozole and tamoxifen in the adjuvant treatment of hormone-receptor-positive, postmenopausal patients with early breast cancer, using the typical patient from the ATAC trial over a lifetime horizon and the Canadian public healthcare perspective. In that study, resource utilization was drawn from Statistics Canada, supplemented by an expert panel. According to their model, patients treated with anastrozole incurred additional treatment costs, compared with patients receiving tamoxifen, but these costs were partially offset by reduced recurrences of breast cancer. Patients treated with anastrozole were projected to experience absolute reductions of 5.6% in the risk of first breast cancer recurrence and 2.8% in the risk of death from breast cancer. This corresponded to 30,000.00 Canadian dollars per life-year gained and 28,000.00 Canadian dollars per quality-adjusted life-year gained. The authors concluded that anastrozole therapy is effective and cost-effective as initial adjuvant therapy in this patient population, when compared to tamoxifen.

Other studies have assessed the economic impact of adjuvant treatment with anastrozole, when compared with tamoxifen, in different healthcare scenarios. Anastrozole was considered cost-effective in the long term in Slovenia and Belgium taking into account the healthcare provider and healthcare system perspectives, respectively. In addition, a second study from Canada using the direct payer perspective concluded that upfront treatment with anastrozole is a cost-effective alternative to 5 years of tamoxifen. Also, based upon ATAC results, and from the perspective of the United Kingdom National Health Service, Mansel et al. have recently shown that the estimated incremental cost-effectiveness of anastrozole compared with tamoxifen was £17,656 per QALY gained. This considered clinical settings similar to the above mentioned studies, with a greater than 90% probability that cost-effectiveness of anastrozole was below £30,000 per QALY gained (the UK threshold). The results of that study were robust for all parameters tested in sensitivity analysis.

The cost-effectiveness of cancer treatment clearly varies across the globally diverse epidemiological and economic spectrum. Despite the fact that novel therapies are typically more expensive than existing alternatives, their prices tend to decrease along the years. In addition, availability of generic medications may further decrease treatment costs. Models such as the one used in this study are quite sensitive to increases in the price of medications. As a corollary to this, decreases in the price ratio between anastrozole and tamoxifen will likely decrease the incremental cost-effectiveness of anastrozole. Also, the cost-effectiveness of any cancer treatment will vary according to patient life expectancy. In Brazil, the life expectancy of women aged 64 is currently 19.3 years.

**Conclusion**

Given the clinical superiority of anastrozole over tamoxifen, and the acceptable incremental cost-effectiveness of this strategy shown in several studies and confirmed in this one, our analysis suggests that upfront treatment with anastrozole for 5 years may be the preferred adjuvant strategy for postmenopausal Brazilian women with hormone-receptor-positive, early breast cancer.

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RESUMO

Custo-efetividade do anastrozol em comparação com tamoxifeno no tratamento adjuvante do câncer de mama precoce no Brasil


Métodos. Para comparar a custo-efetividade dos tratamentos com tamoxifeno ou anastrozol, foram analisados os resultados médicos e econômicos em uma coorte hipotética de mulheres com 64 anos de idade, considerando o sistema de saúde Brasileiro em 2005, sob a perspectiva do setor privado e o horizonte de tempo de uma vida. Usamos dados do Estudo ATAC, um modelo de Markov, um painel de Delphi modificado, e micro-costing (em reais R$) para estimar os custos e a efetividade das duas estratégias.

Resultados. O modelo estimou um ganho de 0.55 anos de vida descontados para pacientes recebendo anastrozol em relação àquelas tratadas com tamoxifeno. Com um custo marginal de R$ 15.141,15, o modelo estimou que o custo-efetividade do anastrozol em relação ao tamoxifeno era de R$ 27.326,80. As simulações de Monte Carlo mostraram que aproximadamente 50% dos casos estavam abaixo do limite de R$ 29.229,00 por ano-vida ganho, que é o recomendado pela Organização Mundial da Saúde para o Brasil.


References