Original Article

COST-EFFECTIVENESS ANALYSIS OF ANASTROZOLE AS ADJUVANT THERAPY FOR BREAST CANCER IN POSTMENOPAUSAL WOMEN

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ABSTRACT

OBJECTIVES. To carry out an economic analysis of the possibility of adoption of anastrozole in Brazil as adjuvant hormone therapy for postmenopausal women with breast cancer.

METHODS. The estimate of the cost-effectiveness of anastrozole in comparison to tamoxifen for postmenopausal women was calculated from three different perspectives: private patients, health insurance plans, and the government (in the form of the Brazilian National Health Service - SUS). A Markov model was designed for a hypothetical cohort of 1000 postmenopausal women in Brazil, based on data from the ATAC trial after 100 months' follow-up, using outcome projections for a 25-year period. Resource utilization and the costs associated with it were obtained from preselected sources and specialist opinion. Treatment costs varied according to the perspective used. The incremental benefit was also included in the model in order to obtain the cost of each quality-adjusted life-year gained (QALY).

RESULTS. Extrapolation of observed benefits over a 25-year period arrived at an estimate of 0.29 QALY gained if anastrozole is used instead of tamoxifen. The cost-effectiveness ratio per QALY gained depended on which perspective was used. There was an increment of R$32,403.00/QALY from the government/SUS perspective, R$32,230.00/QALY for health insurance plans, and R$55,270.00/QALY for private patients.

CONCLUSION. The benefit of using adjuvant anastrozole with postmenopausal patients with post-surgery breast cancer is linked to major differences in the cost-effectiveness ratio and varies depending on perspective. According to current WHO parameters, the increment is considered acceptable from the perspective of the public healthcare system and the health insurance companies, but not from that of private patients.

KEYWORDS: Tamoxifen. Aromatase inhibitors. Adjuvant chemotherapy. Breast cancer. Neoplasms. Cost-effectiveness analysis. Markov chains.

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INTRODUCTION

Currently, breast cancer affects more women worldwide than any other neoplasm and it is the principal cause of death among them. Estimates published by the *Instituto Nacional do Câncer* (INCA) indicate that approximately 50,000 new cases of breast cancer were expected to be detected during 2008 in Brazil.[1] However, little is known about the characteristics of Brazilian patients with breast cancer. The Hospital Cancer Register for the *Fundação Oncocentro do Estado de São Paulo* (FOSP) shows that more than 80% of the 7,000 cases of breast cancer diagnosed in the State during 2006 and 2007 were detected when the disease was in stage I, II or III.[2] these cases are considered potentially curable using surgery plus supplementary treatments, known as adjuvant therapies, which may be any of, or a combination of, radiotherapy, chemotherapy and/or hormone therapy.

One important characteristic of breast cancer which is used to guide the choice of treatment is tumoral expression of hormone receptors (estrogen or progesterone). Approximately 75% to 80% of patients with neoplasms in the breast have tumors that are positive for hormone receptors.[3] Published data demonstrate that women with potentially curable cases of the disease and whose tumors do express hormone receptors benefit from the use of adjuvant hormone therapy.[4] Tamoxifen is an anti-estrogen agent which binds to the estrogen receptors that are found in a proportion of breast cancers. This interaction results in a blockade of processes that are fundamental to cell transcription and of transduction signaling pathways that are necessary to cell growth and proliferation.[5] It was developed in the nineteen seventies and is a well-established option for adjuvant hormone therapy. Among women whose disease is detected at an early

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stage and who are positive for hormone receptors, a compilation of extant studies shows that treatment with tamoxifen for 5 years is associated with an annual reduction in breast cancer mortality of 31% when compared with no treatment.[4]

anastrozole is an aromatase inhibitor that has been developed more recently and whose mechanism of action is by blocking the conversion of adrenal androgens into estrogens. The efficacy and safety of anastrozole, as compared with tamoxifen as initial adjuvant treatment for postmenopausal women, were evaluated in a large scale randomized multicenter study entitled "'Arimidex', Tamoxifen, Alone or in a Combination" (the ATAC study).[6,7] The results after a median follow-up of 100 months demonstrated that patients given anastrozole enjoyed a longer disease-free period (Hazard Ratio: 0.85; p=0.003) and suffered a lower incidence of certain adverse events during treatment.[6,8] Many different authors have recommended using anastrozole rather than tamoxifen as adjuvant treatment for breast cancer in postmenopausal women.[9]

Notwithstanding these benefits, initial use of aromatase inhibitors involves new concerns because of its toxicity profile.[10] The ATAC long-term safety analysis demonstrated that patients taking anastrozole had an increased incidence of bone mass loss, arthralgia and fractures.[7,11] Furthermore, anastrozole use is also associated with a three-times greater risk of hypercholesterolemia.[11]

In addition to the concerns over these new side effects, the costs involved in introducing anastrozole into daily clinical practice is also a cause of controversy worldwide. Breast cancer is a neoplasm with high incidence rates and, as a result, the costs associated with its treatment have a major impact on healthcare system budgets, whether they be public or private systems. Currently, systemic treatments, whether chemotherapy or hormone therapy, are responsible for a large proportion of the costs incurred treating patients with breast cancer. Since the increase in healthcare costs is a worldwide phenomenon, in many developed countries economic assessments have become the rule before approval will be granted by regulatory bodies. In developing countries, such as Brazil, where the financial resources available for healthcare are even more limited, it is imperative that the costs involved with the potentially greater efficacy and effectiveness of a new antineoplastic drug are assessed.[12] Nevertheless, cost-effectiveness analyses are still not the rule within Brazilian healthcare systems.

Brazil has its own peculiarities and the private and public healthcare systems are highly interconnected. Medical care costs have traditionally been divided between the government, health insurance plans and individual patients. Very few patients are able to pay for all of their medical costs and the majority use the public and private healthcare systems in conjunction.[13] Technological innovations have also had an impact on all levels. As the costs of new technologies are incorporated into health insurance plans, fewer people have the financial capacity to pay for these plans and more people become dependent on the government to provide access to healthcare. When costs are assumed by the government, fixed budgets lead to restricted access to high cost technologies and, sometimes, even to social and preventative programs. This cycle increases even further the need for formal cost-effectiveness analyses to be undertaken before new technologies are adopted in our country. Such assessments should theoretically evaluate a perspectives that could possibly influence acceptance of the costs of adopting a new drug.

Cost-effectiveness analyses of the use of anastrozole as an adjuvant treatment for breast cancer have been published from the perspective of the societies in other countries, such as Great Britain,[14] Belgium,[15] the United States[16] and Canada.[17] These studies have concluded that, from the perspective of their respective countries, anastrozole is a cost-effective treatment that is comparable with other antineoplastic treatments that are accepted in general routine oncology.[14-17]

No studies have been published in Brazil on the subject. The lack of conclusive data and the nonexistence of studies comparing the perspectives of the government, the health insurance companies and the individual patients, demand that a cost-effectiveness analysis be undertaken reflecting the situation in Brazil, which can then be used to answer important questions.

Methods

The ATAC study[7] recruited postmenopausal women with early-stage invasive neoplasms of the breast who had completed primary treatment (surgery ± radiotherapy ± chemotherapy) and who were eligible for adjuvant hormone treatment and randomized them to receive anastrozole or tamoxifen or both every day for 5 years. Since an early assessment showed that the branch of the study using both drugs did not exhibit benefits over tamoxifen in terms of efficacy and safety that branch was discontinued and so the analysis presented here is based only on the two single treatment groups (tamoxifen or anastrozole).

Model

TreeAge Pro Suite 2008 (TreeAge Software Inc., Williamstown, MA, USA) was used to develop a probabilistic Markov model,[18] projecting outcomes for a hypothetical cohort of 1000 postmenopausal women, aged 64, with neoplasms of the breast positive for hormone receptors and treated in Brazil. The Markov model assumes that a patient is always in one of a finite number of predefined health states, and that all possible events are represented as transitions from one state to another. The model constructed for this study projected events up to a 25-year horizon.

At a given point in time, the women in this model are allocated to one of six health states: 1) on adjuvant hormone treatment (in this case, anastrozole or tamoxifen); 2) off treatment, in remission; 3) locoregional relapse; 4) distant metastasis; 5) death caused by breast cancer or 6) death from other causes (Figure 1). All of the women enter the model in the "in treatment" state and move between health states in 6-month cycles.

Probabilities and costs

Rates of events for relapse and death from breast cancer were derived from the ATAC study and extrapolated for 25 years. The probabilities of other variables, such as adverse events and dropouts were taken from the ATAC results published after 100 months' follow-up[6,7,11] and can be found in Table 1. The probability

Figure1. Markov model for health states

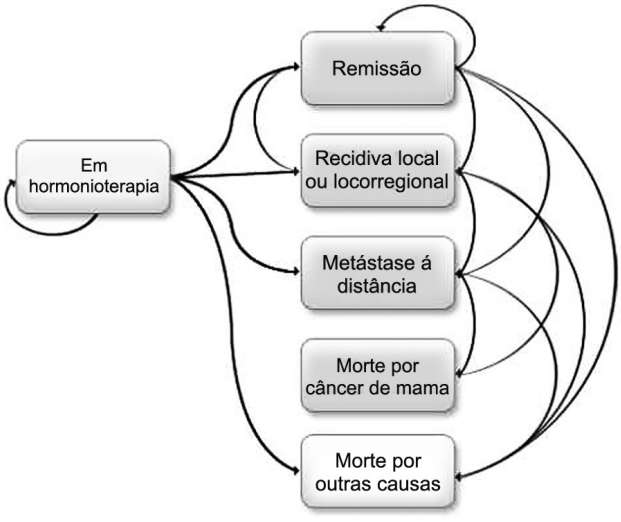

Table 1. Coefficients for the probability of transition (per cycle) extracted from the results published by the ATAC[6,7,11] study and employed in the Markov model

Outcome	Coefficient of probability
Locoregional relapse Tamoxifen anastrozole	0.003422 0.002006
Distant metastasis Tamoxifen anastrozole	0.008883 0.007567
Metastasis after locoregional relapse 1 - 5 years > 5 years	0.048 0.036
Death after metastasis	0.0090
Death from other causes 64-69 years 70-74 years 75-79 years 80-84 years 85-89 years 90-94 years 95-99 years 100 years	0.02089 0.03368 0.05202 0.08507 0.13604 0.21276 0.32541 0.48674

of death from causes other than breast cancer was calculated from WHO data on the life expectancy of the female population within different age groups (from 2006). Coefficients for the probability of distant metastasis occurring after locoregional relapse were obtained from a study published by Kamby and Sengelov.[19]

Consumption of resources such as follow-up tests and specific treatments for each health state and adverse event was estimated for each of the groups analyzed on the basis of specialist opinion.

Table 2. Costs used in cost-effectiveness analysis for the three different perspectives: government, health insurance companies and private patients

Costs	Government	Health insurance plans	Private patients
Medications	All	Some	All
Supplementary tests	All	All	None
Adverse effects	All	All	None
Relapse	All	All	Some

Table 3. Estimated costs per cycle (6 months) used in the model, including costs related to essential tests and to adverse events. (Sources: APAC, ABCFARMA magazine,[20] CBHPM[21])

	SUS	Health insurance plans	Private patients
Cost of Tamoxifen (including the drug itself, tests and adverse events)	R$ 563.67	R$ 296.23	R$ 498.23
Cost of anastrozole (including the drug itself, tests and adverse events)	R$ 1,929.10	R$ 2,533.51	R$ 2,400.69
Cost of follow-up	R$ 20.60	R$ 82.87	-
Cost of locoregional relapse	R$ 2,558.67	R$ 9,882.08	-
Cost of distant metastasis	R$ 4,717.34	R$ 22,119.00	-
Cost of death	R$ 324.91	R$ 2,800.00	R$ 2,500.00

The costs accruing from use of these resources were assessed from three different perspectives – from the point of view of the government, (in the form of the Brazilian National Health Service - SUS), health insurance and private patients. For the SUS perspective, the costs of medications and tests were taken from the official table for authorization of high-cost and complex procedures (APAC) and from the SIA/SUS table of procedures, April 2005 edition. The health insurance perspective was assessed by taking the costs of medications as the highest price offered to the public in issue 198, from February of 2008, of the periodical ABCFARMA[20] and taking the medical fees and supplementary tests from the fifth edition of the Hierarchical Classification of Medical Procedures (CBHPM, *Classificação Hierarquizada de Procedimentos Médicos*)[21]. For the private patients' perspective, the costs of medications were taken as the lowest price quoted by the medication distribution market in the city of São Paulo in March of 2008. The types of costs included in each perspective are described in Table 2 and the prices are given in Table 3.

Because of the peculiarities of Brazilian healthcare, the costs used for calculations vary depending on the perspective used. In the analysis from the perspective of the SUS, all of the costs analyzed were taken from the APAC price table (in the case of anastrozole, the price paid for the aromatase inhibitor for treatment of metastatic disease was used). In the analysis from the perspective of their health insurance companies, all of the costs involved were included with the exception of the provision of tamoxifen, since currently Brazilian legislation allows home-use medication to be excluded contractually. The cost of supplying anastrozole was included in order to assess the economic viability of changing the policy on contractual coverage specifically for this case. Only direct medication costs were included in the analysis from the point of view of private patients, on the assumption that they would have follow-up tests and treatment for relapses covered either by the SUS or by health insurance.

When relevant to one of the three points of view analyzed in this study, the probabilities and costs of adverse events (hysterectomy, endometrial neoplasm, cerebral vascular accident, deep venous thrombosis and skeletal events) were included in drug costs.

International tables that had been published previously were used to adjust for quality of life the number of years gained through treatment. The mean patient-rated utility scores used in the Markov model were obtained from work published by Sorensen et al. (Table 4).[22] The scores derived from the model were then used to estimate the number of years of life gained adjusted by the quality of that life (QALY). The objective of this analysis was to evaluate the economic consequences of substituting tamoxifen by anastrozole, in terms of the number of QALY gained and the increase in costs per QALY gained. The increase in costs was calculated by taking the difference between the total costs associated with using anastrozole and total costs associated with using tamoxifen and dividing it by the number of QALY gained by using anastrozole, for each of the three different perspectives.[23] An annual reduction of 3% was applied to future costs and benefits.

Results

On the basis of the results of the ATAC study, extrapolated to a 25-year follow-up horizon for subsets of a hypothetical cohort of 1000 patients on tamoxifen or anastrozole, the analysis returned a mean QALY of 16.470 and 16.758 per patient, respectively, giving an estimated gain of 0.288 QALY per patient when using anastrozole.

Table 4. Mean patient-rated utilities used in the model[22]

Utility	Value
Remission of disease, without treatment	0.965
Distant metastasis, palliative treatment	0.288
Locoregional relapse	0.766
On treatment with tamoxifen	0.959
On treatment with anastrozole	0.958

Incremental cost-effectiveness from the perspective of the SUS

Neither strategy is dominant over the other. The costs associated with treatment using anastrozole, with treating its adverse events and with later treatments during relapses were estimated at a little over R$26 thousand, whereas the costs incurred by the tamoxifen group were approximately R$17 thousand, leaving a cost increment of R$9 thousand. The incremental cost-effectiveness analysis arrived at a cost of R$32,403.00 per QALY gained.

Incremental cost-effectiveness from the perspective of health insurance plans

In common with the analysis from the perspective of the government, neither strategy proved dominant over the other. The costs associated with treatment using anastrozole, with treating its adverse events and with later treatments during relapses were estimated at over R$65 thousand, whereas the costs incurred by the tamoxifen group were R$56 thousand. The incremental cost-effectiveness analysis arrived at a cost of R$32,230.00 per QALY gained.

Incremental cost-effectiveness from the perspective of private patients

Once more, neither strategy proved dominant over the other. The costs associated with treatment with anastrozole were estimated at R$20 thousand per patient, whereas the costs associated with using tamoxifen were around R$4 thousand per patient, leaving a cost increment of around R$16 thousand. The incremental cost-effectiveness analysis arrived at a cost of R$55,270.00 per QALY gained.

Discussion

Our analysis shows that the benefits accruing from using anastrozole rather than tamoxifen for adjuvant hormone therapy for women with early-stage breast cancer positive for hormone receptors would translate, over a 25-year period, to a lower number of deaths and improved quality of life. These benefits would represent an approximate incremental cost of R$32 thousand per QALY gained from the perspective of the SUS and from the perspective of their health insurance companies and of R$55 thousand per QALY gained seen from the perspective of private patients.

Cost-effectiveness analyses carried out with cost parameters and, most importantly, from the perspective of the economic situations of other countries have concluded that anastrozole is highly cost-effective as an adjuvant treatment for patients with breast cancer. In the United States, the cost increment calculated was US$ 20,246.00 (approximately R$38,467.40) per QALY gained.[16] In Great Britain, the increment calculated was £17,656.00 (or approximately R$67,092.80) per QALY gained.[14] Within the context of these two countries, these increments are acceptable and comparable with other antineoplastic treatments that have already been approved and incorporated into clinical practice.

In Brazil, however, there is not yet any regulation, recommendation or standard defining what incremental cost would be acceptable for adopting a new healthcare technology. Employing the WHO concept, which is that a value of between one and three times the gross domestic product (GDP) per capita is acceptable, the incremental value to be used in Brazil would be a maximum of R$ 40,500.00 per QALY gained. If we accept this figure as the cutoff for cost-effectiveness, our study demonstrates that adopting anastrozole would be considered cost-effective from the perspective of the SUS and of health insurance plans, but not from the perspective of private patients.

However, if we put the WHO recommendation into perspective and compare this limit of three times the GDP per capita with figures acceptable in more developed countries, it will be observed that this figure of R$40,500.00 per QALY gained may be an overestimation. The current limit for incremental cost-effectiveness accepted in Great Britain is no more than £20 thousand to £30 thousand, which is slightly greater than one times the country's GDP per capita. While the United States does not formally use a limit for adoption of technology, they do have a reference figure of US$ 50,000.00 per QALY gained, which is also equivalent to a little more than one times the GDP per capita. We can trace a parallel with that situation. If we consider one times the GDP per capita as a cutoff for cost-effectiveness in Brazil (R$14,000.00), then using the aromatase inhibitor as adjuvant therapy for postmenopausal women with breast cancer would no longer be cost-effective from any of the perspectives analyzed.

In common with many cost-effectiveness analyses, there are limitations to this study that should be taken into consideration. Our Markov model was constructed based on a randomized international study and includes a certain number of assumptions and estimates. The 25-year time period was chosen because, according to specialist opinion, it represents a period that is acceptable from a clinical point of view, for postmenopausal women with breast cancer. Nevertheless, the incremental cost-effectiveness values would vary substantially if the horizon was shorter or longer, since the costs are generally incurred in the early stages while benefits very often can only be measured later on. Furthermore, we based our assumptions of treatment effect on the relapse curves that continue to diverge after 100 months' follow-up on the ATAC study.[6] It was therefore assumed that anastrozole would offer incremental benefits during the period analyzed in our study. The model may need to be updated if results are published after longer follow-up periods. Including data on clinical course and costs among Brazilian patients originating from a retrospective database or from a prospective study within the adjuvant hormone treatment scenario in Brazil would undoubtedly increase the model's power.

In general, there are still barriers to carrying out cost-effectiveness analyses in Brazil that are integrated with healthcare policies. National data are lacking, whether related to the effects of the interventions investigated or to the quality of life of patients treated in the public and private health systems. There are also no trustworthy records relating to diagnoses and no adequate record of mortality or information on costs met by patients that could be the responsibility of the SUS or of the private healthcare system. As a result, we often have to rely on the experience and opinions of specialists and on the results of studies undertaken with populations are different to ours, in order to be able to estimate benefits and costs.

Although our study found that the incremental cost-effectiveness was acceptable according to WHO standards, there are no cost-effectiveness data from Brazil for other antineoplastic treatments that have been approved here. It would be interesting to compare the use of anastrozole as adjuvant therapy with other oncological treatments that have already been adopted as routine by health insurance plans or the SUS. It is possible that we would observe that the majority of antineoplastic treatments that are available today would not be considered cost-effective according to very restrictive criteria.

In many different countries health-related expenditure has increased drastically. In the majority of cases this has been in association with the adoption of new technologies and treatments. Even in developed countries which have more resources available to spend on the population's health, the cost of treating cancer patients has a major impact on society, on the government and on health insurance plans.[24] However, patients who have been diagnosed with cancer need information and access to the new technologies that do exist, but are not provided with assistance to cover the costs associated with treatment, whether directly (drug costs) or indirectly (transport, lost working days and others).[25]

In Brazil, the decision on who is responsible for paying for the treatment of a cancer patient involves factors that are interrelated in a complex manner. In general, health insurance plans do not cover oral medications, because they are for home-use. However, if the risk of relapse is greater there may be a need for palliative chemotherapy later on and over the long-term. This, in general, is covered by health insurance, in accordance with legislation. Cost-effectiveness analyses such as the one we present here could lead to significant changes in treatment coverage policies within private practice if it were to be demonstrated that oral treatments reduced total costs. In practice, in order to add a new oral drug to clinical routine, currently either the patient takes on the cost burden themselves or seeks support from governmental organizations.

The results of this study are highly relevant to healthcare managers, both in the public and private spheres, and could contribute to the development of a process for the adoption of new healthcare technologies, as is the case of aromatase inhibitors. It is of concern that there is still no routine process in Brazil for analyzing the cost-effectiveness of healthcare technologies, and that there are no regulations for making formal recommendations. It is of fundamental importance to initiate a movement to stimulate critical thinking and publicize strategies for rationalizing expenditure, without prejudice to patients. The final result would be the creation of improved health services for the Brazilian population.

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