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Economic Evaluation of Anastrozole Versus Tamoxifen for Early Stage Breast Cancer in Singapore

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A B S T R A C T

Objectives: In Singapore, breast cancer is the leading female malignancy and its incidence has increased threefold over the past decades. For treatment of postmenopausal, hormone receptor positive early stage breast cancer, tamoxifen or aromatase inhibitors such as anastrozole are prescribed either as first-line therapy or sequentially. Currently, anastrozole is patented with a higher drug cost compared with tamoxifen. Hence, the aim of this study was to conduct an economic evaluation of anastrozole versus tamoxifen in early stage breast cancer. **Methods:** A Markov model with a lifetime horizon was developed by using results from the Arimidex, Tamoxifen, Alone or in Combination trial. Direct medical costs were estimated by billing data obtained via financial electronic databases. Utility scores were elicited from 20 experienced oncology nurses using the visual analogue scale. Cost per quality-adjusted life-years was calculated by using the societal perspective. A discount rate of 3% for both charges (expressed in 2010 Singapore dollars) and benefits was used. **Results:** At an additional cost of S $17,597, anastrozole treatment resulted in a gain of 0.085 life-year survival and 0.154 quality-adjusted life-year. The incremental cost-effectiveness ratio of anastrozole was S $207,402 per life-year gained and S $114,061 per quality-adjusted life-year gained compared with tamoxifen. **Conclusion:** This is the first economic evaluation that used 10-year results from the Arimidex, Tamoxifen, Alone or in Combination trial and utility elicited from the local population. If the World Health Organization's recommendation of 1 to 3 gross domestic product range is an acceptable threshold, anastrozole is deemed cost-effective compared with tamoxifen in the treatment of early stage breast cancer.

Keywords: anastrozole, breast cancer, cost-effectiveness analysis, cost-utility analysis, tamoxifen.

Introduction

In Singapore, there are more than 6000 newly diagnosed cancer cases annually [1]. Breast cancer is the leading female malignancy and constitutes approximately 30% of all female cancers [2]. Although there has been a threefold increase in breast cancer incidence between 1968 and 2002 [3], the mortality of breast cancer patients has decreased over the years. The 5-year age standardized relative survival was 46.1% from 1973 to 1977 compared with 76.1% from 1998 to 2002 [4], which has translated to an increasingly high cost of illness for breast cancer that amounts to billions of dollars each year [5–7]. An estimated lifetime per-patient cost of breast cancer was reported to be between US $20,000 and US $100,000 [8]. The treatment cost of cancer has been escalating and will continue to increase, especially with the discovery of new targeted drugs that would have a significant impact on health care resources [9,10]. Because health care resources are often limited, it would be prudent to choose the most cost-effective treatment for patients to ensure that resources are efficiently allocated [11].

Endocrine therapy is one of the main treatment modalities for breast cancer and approximately two-third of all breast cancer patients are required to receive treatment with endocrine therapy [12]. Tamoxifen has been advocated as the gold standard of endocrine treatment over the past few decades and has been shown to improve both disease-free survival (DFS) and overall survival [13,14]. One of the major drawbacks, however, is its unfavorable side-effect profile such as vaginal bleeding and/or discharge, endometrial cancer, and thromboembolic events.

The third-generation aromatase inhibitors (AIs), such as anastrozole, are an attractive alternative treatment option among postmenopausal patients. Currently, there is no consensus regarding the duration of therapy with AIs or the optimal sequence for administration. Nevertheless, numerous clinical practice guidelines from the American Society of Clinical Oncology, National Comprehensive Cancer Network, and St. Gallen International Expert Consensus on the primary treatment of breast cancer have advocated the use of AIs as part of adjuvant treatment for postmenopausal hormone receptor (HR)-positive early stage breast cancer patients [15–17]. AIs can be prescribed as front-line

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therapy, sequential with tamoxifen, or as extended therapy after 5 years of treatment with tamoxifen.

A large randomized controlled trial, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) [18–21], has demonstrated both the efficacy and tolerability of anastrozole as the first-line endocrine therapy for postmenopausal HR-positive breast cancer patients. Anastrozole has been shown to significantly prolong DFS and reduce the rates of breast cancer recurrences. This trial led to the approval of anastrozole by the US Food and Drug Administration for adjuvant treatment of HR-positive early stage breast cancer. Anastrozole has a different side-effect profile compared with tamoxifen and can cause musculoskeletal side effects such as myalgia, arthralgia, and bone loss that can adversely affect the health-related quality of life (HRQOL) of patients [22]. Currently, anastrozole is still patented, and its drug acquisition cost is estimated to be approximately 25 times higher than that of tamoxifen (National Cancer Centre, personal communication, June 2010). The high drug cost would greatly increase the cost of adjuvant therapy, because most patients require 5 years of anastrozole treatment.

Although multiple studies have investigated the cost-effectiveness of various AIs compared with that of tamoxifen [23–29] in Belgium, Brazil, Canada, Germany, the United Kingdom, and the United States and reported that anastrozole is cost-effective compared with tamoxifen, none have been conducted in Singapore. It is essential to perform an economic evaluation of endocrine therapy in breast cancer patients in Singapore because health care systems and utility scores of patients could differ among countries, and therefore it may not be appropriate to extrapolate previous published study results to our local population. Hence, the objective of this study was to conduct an economic evaluation of anastrozole, the first AI approved for adjuvant treatment of postmenopausal women with HR-positive early stage breast cancer, in comparison with tamoxifen by using the ATAC trial as the main source of effectiveness data. Anastrozole was chosen because the ATAC trial is the largest adjuvant trial with the longest follow-up data to date. The results of this study are valuable because they can assist in health care resource allocation and aid physicians' decision making during prescribing.

Methods

In the ATAC trial, postmenopausal patients with invasive operable breast cancer were randomized to anastrozole, tamoxifen, or a combination of both for up to 5 years on completion of primary therapy (surgery ± radiotherapy ± chemotherapy). The combination arm failed to show any benefit in terms of efficacy or side-effects tolerability over tamoxifen alone. The primary end points of the study were DFS and occurrence of adverse effects. After a median of 10 years, anastrozole was demonstrated to improve DFS, time to recurrence, and time to distant recurrence when compared with tamoxifen.

A Markov model was constructed by using TreeAge Pro 2009 (release 1.0.2) (TreeAge Software, Inc, MA) based on ATAC trial data. A hypothetical cohort of 1000 postmenopausal women (mean age of 64 years) with HR-positive early stage breast cancer who had completed primary therapy and who were eligible for adjuvant endocrine therapy was used in the model. The patients were followed for a lifetime horizon.

A societal perspective was taken but only direct medical costs were included in the analysis. Indirect costs were not included in this study because the mean age of the patients was 64 years and hence most were not likely to be working. Costs were expressed in 2010 Singapore dollars. Costs and benefits were both discounted at 3% per year.

Model structure

The structure of the Markov model is shown in Figure 1. A total of five mutually exclusive health states were defined as no recurrence (NR), locoregional recurrence (LR), distant recurrence (DR), death from breast cancer, and death from other causes [24]. Each cycle represented 1 year. All patients were assumed to enter the model under the "no recurrence" health state. At the end of each cycle, a patient could either remain at the same health state or move to a different health state on the basis of ATAC trial results. However, patients at absorbing health states (i.e., death from breast cancer or other causes) were not allowed to move to other health states. In addition, patients could only be in one of the five defined health states at a time and these patients were not allowed to switch between treatment arms.

Model inputs

Data inputs were obtained from the 10-year analysis of the ATAC trial [18], interviews with oncology nurses, local financial electronic databases, and published literature.

Recurrence rates for breast cancer were obtained from the ATAC trial and published literature [18,24]. Using these recurrence rates, the respective probabilities of general, local, and distant recurrences were calculated (Table 1). Percentages of patients who experienced adverse events (AEs) were obtained from the ATAC trial [20]. The risk of AEs was assumed to be constant over the 5 years of treatment. Mortality rates due to breast cancer after recurrence were assumed to be similar and constant for both anastrozole and tamoxifen [25]. The age-dependent mortality rates for all causes of the general female population were obtained from the Department of Statistics, Singapore (Table 1) [30].

Resource utilization and costs

The National Cancer Centre (NCCS) is the largest ambulatory cancer center in Singapore that treats approximately 70% of all cancer patients. A retrospective cohort of postmenopausal, HR-positive early stage breast cancer patients treated at the NCCS with either anastrozole or tamoxifen adjuvant therapy from January 2001 through December 2009 was reviewed. Patients' medical records (both electronic and hard copy) as well as medication dispensing records from the pharmacy department were accessed. These patients were then allocated into the three respective different health states (NR, LR, and DR).

Direct medical costs were estimated from billing data obtained via financial electronic databases of the NCCS and the Singapore General Hospital. These medical costs included physicians' consultation fees, costs of scans, laboratory, and procedures, drug costs, treatment costs for AEs, and hospitalization (Table 2). In this study, costs for the NR state for both anastrozole and tamoxifen included only major costly AEs such as endometrial cancer, spine fracture, ischemic cardiovascular events, and venous thromboembolism. The cost data were obtained via *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes from the Singapore General Hospital. All costs were inflated to 2010 costs by the Singapore consumer price index (health care component) based on first and second quarter values [31].

Utility measurement

There are various methods to obtain utility values, namely, direct measurement, published literature, or expert opinion. Although there is no preferred method, direct measurement can overcome potential bias from the other two methods due to imprecise estimates and bias from the selection of literature to be used. A targeted literature review was conducted to identify the adverse-effect profiles of endocrine therapies and their impact on various health-related quality-of-life aspects. A total of 20 hypothetical health states and their descriptions were developed and under-