Pharmacoeconomic aspects of adjuvant anastrozole or tamoxifen in breast cancer: a Slovenian perspective

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New treatment approaches that include the use of aromatase inhibitors in adjuvant breast cancer management are associated with higher efficacy and increased drug costs. Our aim was to calculate the difference in total costs of care associated with two therapeutic options, anastrozole and tamoxifen, from the perspective of a healthcare provider. The cost of care and a decision tree analysis were used in this assessment. The efficacy of both drugs in terms of relapse rate was obtained from an ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after the median observational time of 68 months. The total sum of all direct healthcare costs over a 60-month period was 14 438 and 8009 Euros per person in the anastrozole and tamoxifen arm, respectively. Despite higher total costs of care associated with anastrozole, the drug cost ratio of anastrozole/tamoxifen = 8.1/1 converted to a ratio of only 1.75/1 in favor of tamoxifen when costs of recurrence and adverse events were included. The total costs of care, including disease recurrences and adverse event management obtained in our analysis were similar to total costs of care values for other surveys, which lead us to believe that anastrozole is also a cost-effective alternative to tamoxifen in Slovenia. *Anti-Cancer Drugs* 17:719–724 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:719–724

Keywords: adjuvant hormone therapy, anastrozole, breast cancer, pharmacoeconomics, tamoxifen

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Received 2 December 2005 **Revised** 23 February 2006
Accepted 24 February 2006

Introduction

Cancer is significant in terms of incidence, prevalence, mortality, morbidity and costs [1]. Breast cancer is the most common form and the leading cause of cancer death in women. Nine hundred sixty-four new cases and 380 deaths from breast cancer diagnosed in Slovenia in 2001 were recorded. The incidence is rising by approximately 3% annually and has reached a level of 94.7 cases per 100 000 population [2]. On the other hand, more women now survive breast cancer and for longer periods of time than ever before. Therefore, the prevalent population has grown substantially, which means that the economic burden of breast cancer is also changing [3]. Although the incidence and prevalence of early breast cancer (EBC) and metastatic breast cancer are well established, there is limited information on the direct, indirect and intangible costs reported even for advanced, let alone for early, breast cancer [1].

Adjuvant systemic therapy has improved the prognosis of women with EBC significantly. In hormone receptor-positive (HR +) patients, the use of endocrine treatment with tamoxifen (TAM) was found to reduce the frequency of relapse and mortality by 41 and 33%, respectively [4]. A third generation of aromatase inhibitors such as anastrozole (AN), letrozole and exemestane, however, has challenged its position in postmenopausal women. After a median follow-up of 33 months, the first results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial have shown the significant advantages of AN in terms of decreased risk for all first events observed in terms of local, contralateral and distant recurrence [5]. A longer follow-up period confirmed this observation. The absolute 1.7% reduction in the rate of relapse observed after 33 months increased to a 3.7% reduction observed after a median observational time of 68 months for HR + patients [6].

Despite the fact that trials with AN provide the most mature and extended data with respect to aromatase inhibitor use in an adjuvant setting, there are also trials investigating the role of other aromatase inhibitors in EBC treatment. The trial with letrozole indicated that there is a benefit in giving an aromatase inhibitor to patients who have concluded the standard 5 years of treatment with TAM [7]. A few other trials with exemestane and AN indicate that patients currently on TAM therapy for 2–3 years benefit from switching to an aromatase inhibitor compared with a group that continued with TAM therapy for up to 5 years [8,9].

The literature search of Medline and Cochrane databases shows that only a few cost analyses in adjuvant therapy of EBC have been published. The majority of data found

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were cost analyses based on ATAC trial data. AN was found to be a more cost-effective alternative to TAM in Canada, the UK and the US [10–12]. A cost analysis of extended adjuvant letrozole, based on MA-17 (NCIC CTG Intergroup Trial MA-17: a randomized trial of letrozole in postmenopausal women after 5 years of tamoxifen therapy for EBC) data, also showed that extended letrozole use is cost effective [13].

Promising data arising from ATAC trial encouraged us to conduct our own analyses adjusted to Slovenian healthcare system. The primary goal of the study was to calculate the difference in total costs of care (TCC) associated with both therapeutic options AN or TAM from the perspective of a healthcare provider.

Materials and methods

A cost of care analysis and a decision tree analysis were used in this assessment [14]. The efficacy of both drugs in terms of relapse rate was obtained from an ATAC trial after the median observational time of 68 months. According to this data, the estimated rates of local, contralateral and distant relapse were 1.38, 1.12 and 10.37% for AN, and 2.05, 1.89 and 12.03% for TAM, respectively [5]. All direct healthcare costs were obtained from the Institute of Oncology, and other university and general hospitals. Expenditures for adverse event management, disease progression, treatment of a primary EBC and contralateral breast cancer (CBC) were summarized to obtain overall costs. Evaluating costs associated with the loss of human life was avoided and therefore not considered in this analysis. The hypothetical cost of care calculation was carried out for 450 postmenopausal women with EBC, which is the approximate number of new cases per year in Slovenia. The analysis took into consideration all costs arising in the period of 60 months, which was consistent with the treatment's duration time reported in the ATAC trial.

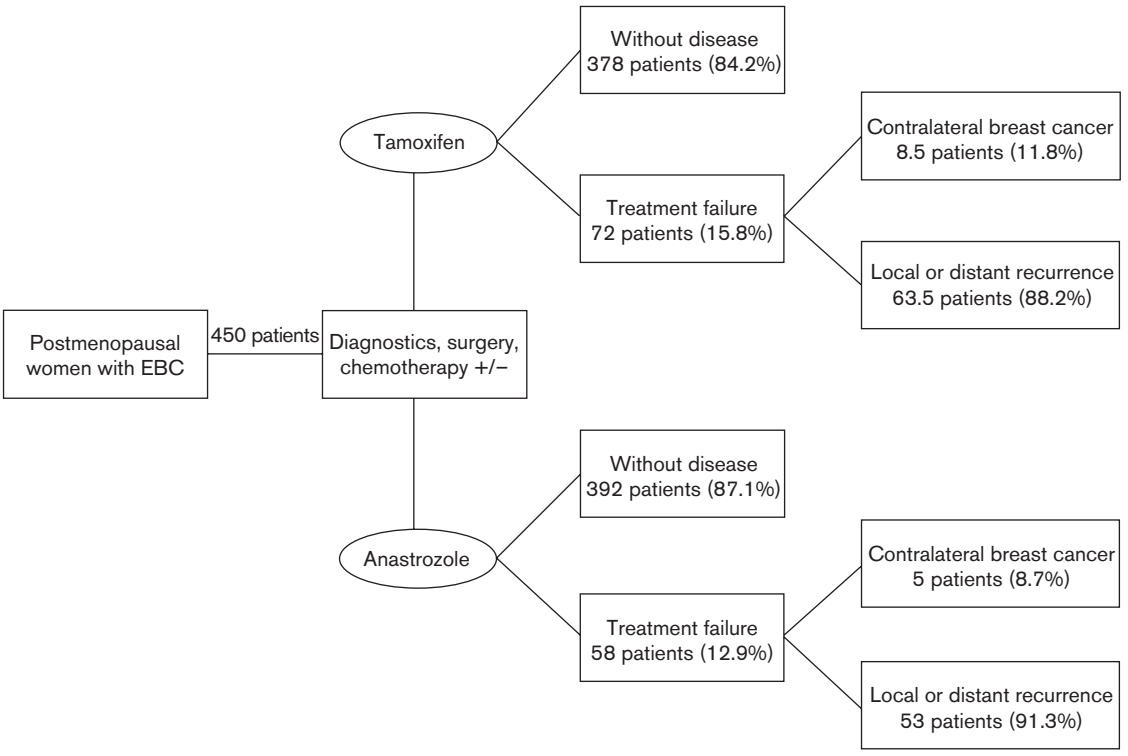
Cost of care analysis

An enumeration of the healthcare resources consumed and the costs of providing care to a given patient population over a chosen time were considered and combined in a cost of care analysis that compared AN and TAM. The primary outcome determined in the study was the difference in the TCC associated with each treatment option.

Decision tree analysis

We used a decision tree analysis to model the treatment of postmenopausal women with HR + EBC with either AN or TAM. The model is based on data obtained from the ATAC trial and a methodology that is described in the sections that follow. It begins at the decision node, where

Fig. 1



Decision tree model.

all patients conclude primary treatment consisting of surgery, with or without radiotherapy, with or without chemotherapy, and where a choice has to be made between AN and TAM. All 450 patients, the approximate number of new cases per year in Slovenia, would receive either AN 1 mg or TAM 20 mg on a daily basis. After the 60-month treatment period, two major outcomes were assessed. Patients were either disease free or their treatment had failed. In the case of treatment failure, patients could have experienced disease recurrence, local or distant, or an occurrence of CBC. The absolute number of patients with or without disease experiencing either local, distant recurrence or CBC was calculated with regard to the rate of recurrences in the ATAC trial in the 68-month follow-up period (Fig. 1).

Estimate of treatment costs

Estimate of costs related to primary early breast cancer treatment

All patients diagnosed with primary EBC in the period of 1997–2000 were treated according to the guidelines established at the Institute of Oncology. This enabled us to conduct an average cost calculation of treatment per patient to the point at which hormonal therapy needs to be introduced. Cost calculation was based on data obtained by the Analytical Department and the Hospital Pharmacy at the Institute of Oncology. Data included details of clinical examination, mammography, preoperative diagnostics and laboratory tests, surgery, days spent in hospital and the outpatients' unit, and radiotherapy and chemotherapy.

Estimate of costs related to primary early breast cancer treatment of the contralateral breast

If a primary EBC of the contralateral breast occurred, the treatment related to this condition was considered the same as treatment of the first primary EBC. Therefore, total costs related to CBC treatment are the same as those calculated for the first primary EBC (Table 1).

Estimate of costs related to disease recurrence

The costs related to disease progression were estimated by a model group of 20 randomly assigned patients chosen from the patients' database treated at the Institute of Oncology between years 1997 and 2000. All patients were postmenopausal women with HR + EBC, whose disease had progressed in primary therapy. The period chosen to calculate the direct medical and non-medical costs related to disease recurrence was 60 months, the same as the treatment duration time in the ATAC trial. Average medical costs were then calculated through the medical charts of 20 patients. Medical costs consisted of outpatient visits, hospital care, diagnostic procedures (computed tomography, ultrasound, RTG; mammography, lab tests, etc.), medical treatment and radiotherapy (Table 2). Non-medical costs included transportation, home care and medical aids such as wigs (Table 3).

Table 1 Costs related to the treatment of first primary early or contralateral breast cancer

Service	Average cost per person (Euro)
Clinical examination, mammography, cytology	138
Preoperative diagnostics	191
Surgery	2155
Hospital care and ambulatory care unit	609
Radiotherapy after quadrantectomy	1070
Radiotherapy after radical mastectomy	392
Chemotherapy	809
Total	5364

Surgery includes surgery, anesthesia and pathohistological examination of the primary tumour; chemotherapy includes only the cost of the drug.

Table 2 Direct non-medical costs related to disease recurrence

Service	Average cost per person (Euro)
Home care	16
Transportation	1273
Medical device	33
Total	1322

Table 3 Direct medical costs related to disease recurrence

Service	Average cost per person (Euro)
Haematology and biochemistry	481
Radiological examinations	579
Nuclear medicine examination	107
Pathohistological examination	217
Outpatient visit	513
Hospitals care	2006
Radiotherapy	514
Drugs	3744
Total	8161

Direct medical and non-medical costs were evaluated by using data acquired at the Health Insurance Institute of Slovenia, the National Formulary of Drugs, and the Hospital Pharmacy and Analytical Department of the Institute of Oncology. The Institute of Oncology is the only national health center for cancer research and treatment in Slovenia, so it is a valid source of data for the assessment of costs in this paper.

Adverse events

The latest publication of the ATAC data revealed that AN was associated with fever adverse events more than TAM, especially in terms of gynecological problems and vascular events, but with an increased fracture rate and arthralgia. As a result of the many adverse events reported in the trial, a decision was made to evaluate only the costs of managing severe adverse events such as spinal fractures, deep vein thrombo-embolic and ischemic cerebrovascular events, and costs associated with gynecological disorders for which hysterectomy was needed. Cost assessment took into consideration all expenditures associated with specific conditions, including operative procedure, additional medication, blood transfusion, hospital care, etc.

Sensitivity analysis

A multi-way analysis was chosen, in which we varied the prices of both drugs used in the treatment settings. A different percentage rate was used in each variable parameter. The data were then combined, and used to create and evaluate a base, the worst and the best possible outcomes. New overall treatment cost ratios were calculated for each of these and compared with the base value.

Results

In the present study, the direct medical costs of first primary EBC and CBC were calculated with the direct medical and non-medical costs of disease recurrence. Using primary EBC treatment guidelines and the medical charts of 20 patients, we calculated an average cost per patient, which amounted to 9483 Euros for disease recurrence and 5364 Euros for first primary and primary of the contralateral breast, as well. Both figures were then used in the decision tree model, which enabled us to calculate an overall cost for each simulated path of treatment. The average cost of primary breast cancer treatment per patient treated between 1997 and 2000, according to the current guidelines at the Institute of Oncology in Ljubljana, are shown in Table 1.

Adjuvant chemotherapy was applied to 36% of postmenopausal women with HR + EBC. The majority of patients, 55.5%, received cyclophosphamide, methotrexate and 5-flourouracil, while 44.5% of patients received anthracycline-based chemotherapy.

The calculation of radiotherapy costs also needs further explanation. Breast conservation treatment with additional radiotherapy was carried out in 25% of EBC cases; the remaining 75% underwent radical mastectomy and 22% of these patients were offered additional radiotherapy. On the basis of these data, the average cost of radiotherapy per patient was calculated.

Medication costs were as follows: TAM 20 mg, 0.53 Euros per treatment day, and AN 1 mg, 4.29 Euros per treatment day.

Direct non-medical and medical costs related to disease recurrence are presented in Tables 2 and 3.

Transportation was the main contributor to the non-medical costs related to disease recurrence. It includes all non-urgent transportation for patients needing any kind of services as described in Table 2.

Table 3 includes all the parameters evaluated in patients with disease recurrence. The drugs that contributed most to the total expenditure for this group of patients consisted of chemotherapeutic agents, hormonal agents, bisphosphonates, antiemetics, haematopoietic growth factors and blood transfusions. Chemotherapy and second- or third-line hormonal therapy amounted to 34.1 and 33.8% of total drug costs. Bisphosphonates, antiemetics, hematopoietic growth factors and blood transfusions, and other drugs such as analgesics amounted to 13.1, 9.5, 5.6 and 3.9% of total drug cost in the management of disease recurrence, respectively.

Table 4 Average cost per patient related to specific adverse event management

Adverse event	Anastrozole (Euro)	Tamoxifen (Euro)	Incremental (Euro)
Spine fracture	125	75	50
Hysterectomy	68	238	−170
Deep venous thrombosis	27	40	−13
Cerebrovascular event	229	322	−92
Total	449	675	−225

Table 4 contains the average cost per patient treated for specific adverse events. Treatment with AN proved to be favorable to TAM in almost all adverse events evaluated, except in the costs of managing spinal fractures.

Table 5 displays overall treatment costs as accumulated in the treatment model, with costs for managing adverse events by using either AN or TAM as a treatment option. As the model predicted three possible outcomes of disease, costs by individual treatment path can also be observed. Cost calculation by individual treatment path reveals that in the first possible outcome in which patients are disease free, larger medical and drug acquisition costs associated with AN resulted in higher overall costs for AN than for TAM in this particular treatment path. A group of patients with recurrent disease treated with AN exhibited lower medical and non-medical costs than those treated with TAM. This advantage was devaluated by the difference in the drug acquisition costs, which resulted in slightly higher overall costs for AN also in this particular path. In the third possible outcome in which patients experienced CBC, lower medical costs were associated with AN, which caused overall costs to be in favor of AN in this particular treatment path in contrast to findings in previous ones. The overall calculation of costs in the model shows that TCC associated with the use of AN were greater than with the use of TAM (14 820 versus 8448 Euros, respectively).

Table 6 presents the effect of possible drug price change to the total cost of care ratio. The scenario analysis points out that alterations in acquisition drug price of AN and TAM cause the total treatment cost ratio to change. The reduction of AN drug price for 10% causes the total treatment cost ratio to decrease to a value of 1.66 and

Table 5 Total cost of care per patient treated with either anastrozole or tamoxifen in the period of 5 years

	Anastrozole (Euro)	Tamoxifen (Euro)	Incremental (Euro)
Path I (without disease)			
medical costs	4673	4507	166
acquisition drug costs	6820	813	6007
Path IIa (recurrent disease)			
medical costs	1593	1909	−316
non-medical costs	156	187	−31
acquisition drug costs	922	136	786
Path IIb (contralateral disease)			
medical costs	120	202	−82
acquisition drug costs	87	18	69
Adverse events			
medical costs	449	675	−227
total costs of care	14820	8448	6372

Table 6 Baseline and sensitivity analysis results for total costs of care per patient

	Anastrozole (Euro)	Tamoxifen (Euro)	Ratio
Base case (A 0%, T 0%, E 0%)	14820	8448	1.75
Worse case (A +10%, T −5%, E 0%)	15602	8398	1.86
Best case (A −10%, T 0%, E 0%)	14038	8448	1.66

A, anastrozole percentage change of daily drug dosage price; T, tamoxifen percentage change of daily drug dosage price; E, efficacy of treatment.

therefore becomes even more in favor of AN treatment. Increasing the drug price of AN for 10% together with a decrease of TAM drug price for 5% causes a change in the opposite direction of the TCC ratio to a value of 1.86.

Daily drug costs of 4.29 and 0.53 Euros for AN 1 mg and TAM 20 mg, respectively, were multiplied by the number of treatment days to give the total acquisition drug cost, which resulted in a drug cost ratio of 8.1/1 in favor of TAM. Nevertheless, the total sum of all direct healthcare costs over the 60-month period was 6.669 and 3.801 million Euros or 14820 and 8448 Euros per person in the AN and TAM arm, respectively. Despite the higher overall treatment costs associated with AN, the drug cost ratio of AN/TAM = 8.1/1 converted to a ratio of only 1.75/1 in favor of TAM, considering TCC. Moreover, this ratio can further be reduced, as seen from the sensitivity analysis results in Table 6, in which the price of both drug regimens were altered positively and negatively.

Discussion

The results from large random multiple trials show that aromatase inhibitors as an adjuvant therapy lower the risk of disease recurrence in HR + EBC patients. Therefore, aromatase inhibitors are expected to be introduced as a standard adjuvant treatment either as an initial therapy or following prior treatment with TAM [15]. The use of aromatase inhibitors in EBC is also supported by the latest international guidelines from St Gallen [16].

In our analysis, the drug acquisition cost ratio of AN/TAM = 8.1/1 converted to a ratio of 1.75/1 in favor of TAM, considering that the TCC comprise disease recurrence management, adverse events and drug costs in the 60-month treatment period. Although AN still resulted in 1.75 times higher TCC, we find the results interesting and an incentive. As observed in Table 5, the drug costs of AN and TAM were 53 and 11% of TCC in the 60-month period. The difference in cumulative acquisition drug costs between AN and TAM over 5 years was partly offset by the lower costs of treating recurrences, CBC and adverse events management. The total drug expenditure for AN and TAM, together with the observed divergence of the recurrence curves during the completed treatment analysis of the ATAC trial, in addition to the tolerability advantages of AN in terms of a significantly lower incidence of withdrawals owing to adverse events (11.1 versus 14.3%, $P = 0.0002$) further support the belief that the TCC ratio will probably decrease and become even less, in favor of TAM. The sensitivity analysis results confirm these predictions to a certain degree, despite the results being robust in the face of variations in the parameters used.

Even though this study focused on the first 5 years of treatment, and did not extrapolate costs and benefits to 25 years like some other studies, similar results are observed. The TCC ratio after 5 years of treatment of 1.75/1 proved to be very similar to the ratio obtained by a UK cost analysis over the same period presented at the American Society of Clinical Oncology 2005 [17]. Furthermore, TCC per patient treated with either AN or TAM, which amounted to 14 820 and 8448 Euros, respectively, was again very similar to the TCC reported in the UK analysis after the first 5 years of treatment. If one could assume the same recurrence rate and extrapolation of the results to 25 years as in the UK analysis, then one could have concluded that the cost per quality adjusted life year in Slovenia is broadly similar to that in the UK.

In contrast to the findings of published pharmacoeconomic studies, AN was associated with higher TCC in all of them; however, costs were still below the national cost-effectiveness threshold and therefore considered cost effective. Unfortunately, the lack of national cost-effectiveness thresholds in Slovenia compels us to directly compare the results with those of other European countries and explain why cost utility analysis was not used in this assessment. Nevertheless, if one could assume similar thresholds for Slovenia, then one would conclude that AN is a cost-effective alternative to TAM in this country.

Acknowledgment

The authors are grateful to Mrs Ana Zlicar from the Analytical Department of The Institute of Oncology for her contribution to the cost evaluation of the treatment model.

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