Cost-Benefit Analysis of Endocrine Therapy in the Adjuvant Setting for Postmenopausal Patients with Hormone Receptor-Positive Breast Cancer, Based on Survival Data and Future Prices for Generic Drugs in the Context of the German Health Care System

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Keywords

Letrozole · Anastrozole · Tamoxifen · Cost-effectiveness · QALY · BIG 1-98 · ATAC

Summary

Background: Cost-effectiveness analyses have focused on aromatase inhibitors (AIs), but the results are inconsistent and disease-free survival has often been extrapolated to overall survival. The present study calculates the cost-effectiveness of 5 years of letrozole versus tamoxifen versus anastrozole in the context of the German health care system, using survival data from the Breast International Group (BIG) 1-98 study and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study and generic prices. **Materials and Methods:** A hybrid model was developed that incorporates recurrence rates, overall survival, treatment costs and treatment-associated adverse events and the resulting costs. The basic assumption was that generic anastrozole would lead to a price reduction to 75% of the original price. Further analyses were carried out with 50% and 25% of the original prices for anastrozole and letrozole. **Results:** The cost-benefit model showed a gain of 0.3124 or 0.0659 quality-adjusted life years (QALYs) for letrozole or anastrozole. Incremental costs of € 29,375.15/QALY for letrozole (100% of original price) were calculated and € 94,648.03/QALY for anastrozole (75% of original price). Marked increases in cost-effectiveness are observed with further decreases in price (anastrozole: 50% price € 54,715.17/QALY, 25% price € 14,779.57/QALY; letrozole 75% price € 20,988.59/QALY, 50% price € 12,602.03/QALY, 25% price € 4,215.46/QALY). **Conclusion:** The present model including the inverse probability of censoring weighted analysis (IPCW) for letrozole and generic prices for both AIs shows that letrozole is cost effective.

Schlüsselwörter

Letrozol · Anastrozol · Tamoxifen · Kosteneffektivität · QALY · BIG 1-98 · ATAC

Zusammenfassung

Hintergrund: Aromatasehemmer (AIs) sind Gegenstand von Kosteneffektivitätsanalysen, die jedoch häufig heterogen sind, bzw. Ergebnisse des krankheitsfreien Überlebens werden auf das Gesamtüberleben extrapoliert. Die vorliegende Arbeit berechnet die Kosteneffektivität von 5 Jahren Letrozol versus Tamoxifen versus Anastrozol aus der Sicht des deutschen Gesundheitswesens mit Berücksichtigung der Überlebensdaten der BIG-1-98-Studie und der ATAC-Studie und dem Patentauslaufen der AIs. **Material und Methoden:** Im Rahmen eines Hybrid-Modells wurden neben Rezidivraten das Gesamtüberleben und die Kosten für Therapie, unerwünschte Ereignisse und Folgekosten integriert. Als Basisannahme wurde für Anastrozol ein Preisabfall auf 75% angenommen. Folgend wurden die Analysen mit 50% und 25% des Originalpreises von Anastrozol und Letrozol kalkuliert. **Ergebnisse:** Das Kosten-Nutzwert-Modell zeigt einen Zugewinn von 0,3124 bzw. 0,0659 QALYs für Letrozol bzw. Anastrozol. Es errechnen sich inkrementelle Kosten von 29 375,15 €/QALY für Letrozol (100% des Originalpreises) bzw. 94 648,03 €/QALY für Anastrozol (75% des Originalpreises) im Vergleich zu Tamoxifen. Bei einem weiteren Abfall der Preise zeigt sich eine deutliche Erhöhung der Kosteneffektivität (Anastrozol: 50%-Preis 54 715,17 €/QALY, 25%-Preis 14 779,57 €/QALY; Letrozol: 75%-Preis 20 988,59 €/QALY, 50%-Preis 12 602,03 €/QALY, 25%-Preis 4 215,46 €/QALY). **Schlussfolgerung:** Das Modell verdeutlicht unter Berücksichtigung der IPCW-Analyse (Inverse Probability of Censoring Weighted Analysis) und dem Patentauslauf für beide AIs eine Kosteneffektivität für Letrozol.

Introduction

Costs in the health care system have been increasing exponentially for years, and Germany is one of the countries with the highest costs for health care [1, 2], with drug costs having risen from € 19.2 billion in 1999 to € 32.4 billion in 2009 [3]. In order to meet this challenge in the longer term, an additional dimension is increasingly being incorporated into medical decision-making – the assessment of costs relative to benefit using health-economic decision-making models. In Germany, following the latest health care reform (the Drug Market Reform Law, *Arzneimittelmarktneuordnungsgesetz*, AMNOG), a rapid evaluation of the benefit of drugs is carried out by the Joint Federal Committee (*Gemeinsamer Bundesausschuss*, GBA) with support from the Institute for Quality and Economic Efficiency in the Health Care System (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG) [4]. A review of published analyses shows that the quality-adjusted life-year (QALY, i.e. an additionally gained year of life with 100% quality of life due to a measure taken) and the incremental cost-effectiveness ratio (ICER, i.e. the costs required to gain 1 QALY through a new form of treatment in comparison with the standard procedure) are continuing to be accepted internationally.

Endocrine therapies in the adjuvant setting for patients with hormone receptor-positive breast carcinoma are an important part of health economics studies. The 5-year prevalence for all women with breast carcinoma over the age of 50 (usually postmenopausal women) is 193,000 in Germany [5]. Assuming that 71.5% of these carcinomas are hormone receptor positive [6], treatment with an aromatase inhibitor (AI) may potentially affect 137,995 women. It is understandable that the benefits of endocrine therapy in comparison with its risks and costs need to be weighed up from the point of view of the health care system.

A 5-year course of treatment with tamoxifen has led to a reduction in the relative risk of recurrence by 50% and an increase in survival by 25% in these patients. However, up to 50% of the women can potentially develop more advanced disease (progression) [7]. In addition, tamoxifen is associated with sometimes severe side effects, such as endometrial carcinoma or thromboses and embolism. By contrast, AIs are more effective than tamoxifen in both metastatic and adjuvant situations [8–11]. Administration of AIs leads to higher direct drug costs, but these agents are also more effective by preventing recurrences and metastases, which may be associated with much higher subsequent costs. Cost-effectiveness analyses can make an important contribution here.

Due to numerous differences between the health care systems, an analysis specific of the health care system in Germany, taking the costs that arise here into account, is necessary. In addition, many cost-effectiveness studies have mingled the results for disease-free survival and overall survival, or have extrapolated the results for disease-free survival to

overall survival, and this has given rise to critical debate. A cost-effectiveness analysis focusing on efficacy relative to overall survival thus appears to be necessary. Furthermore, in 2011, anastrozole was the first AI to become a generic agent, and this will lead to a reduction in the price of the drug.

The present study addresses these aspects and estimates the cost-effectiveness of 5 years of treatment with letrozole and 5 years of anastrozole, each in comparison with 5 years of tamoxifen, in the context of the German health care system and based on the survival data from the Breast International Group (BIG) 1-98 study and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, taking into account the current expiry of the patent for anastrozole and the impending expiry of the patent for letrozole.

Material and Methods

Model

A hybrid model was developed to estimate the cost-benefit ratio of endocrine treatments in adjuvant therapy. The model on the one hand includes recurrence rates and also overall survival with the individual forms of treatment, and on the other hand combines these with a Markov model for the costs of treatment and treatment-associated adverse events and their resulting costs [12]. All of the patients included in the model were postmenopausal and had a hormone receptor-positive breast carcinoma. The results were calculated as costs per QALY. A time period of 20 years was used in order to record the long-term effects of treatment. The discounting rate was 3%, in accordance with the IQWiG recommendations [13].

Efficacy Data

Both locoregional recurrences and distant metastases were defined as disease-specific events. Mortality tables for calculating survival probabilities for the first 7 years were based on the tamoxifen arm of the BIG 1-98 study [8, 9]. Data for cohorts of patients in the Early Breast Cancer Trialists' Group (EBCTG) study who had taken tamoxifen for 5 years were used for survival data for years 8–10 [7]. Survival in years 11–15 was estimated using the annual mortality ratio for years 1–10 in the EBCTG study cohorts. The data from the EBCTG study were chosen here as they are based on larger numbers of patients with a longer follow-up period. For the subsequent years (16–20), general mortality tables for the general population for women aged 76–80 years were used.

Hazard ratios (HRs) for letrozole versus tamoxifen and for anastrozole versus tamoxifen from the studies mentioned above were used to calculate overall survival following treatment with letrozole and anastrozole. The comparison of letrozole versus tamoxifen is based on the HR for the first 7 years, corresponding to the published follow-up from the BIG 1-98 study [9]. The data from the BIG study are based on the inverse probability of censoring weighted analysis (IPCW) [10]. The data for anastrozole versus tamoxifen are based on the published 9-year follow-up data from the ATAC study [11].

It was assumed that the subsequent annual survival probabilities in the 3 groups were identical, as no further data were available here. However, the mortality with the 2 AIs is higher, as more individuals in these groups are alive at the end of the follow-up period than in the group with tamoxifen treatment.

Cost Data

All costs are based on data from the German health care system for the year 2010. The costs of care, diagnosis and treatment were estimated for

outpatients on the basis of the 2010 Standard Assessment Criteria (*Einheitlicher Bewertungsmaßstab*, EBM) (EBM score 3.5048 cents) [14], and for inpatients on the basis of the 2010 diagnosis-related group (DRG) case rate catalog used in the Diagnosis-Related Groups in Germany (G-DRG) system. It was assumed that follow-up care was provided for each diagnosis in accordance with the current S3 guideline [15]. It was also assumed in the calculations that all patients receiving an AI annually underwent a dual-energy X-ray absorptiometry (DXA) scan to check for bone density during therapy, and that all patients receiving tamoxifen therapy underwent a vaginal ultrasound examination every 6 months to check the endometrial thickness.

Drug costs were recorded in accordance with the standard sources [16]. A price of 75% of the current costs was assumed as a basic model for generic anastrozole, in accordance with the question addressed in the model. Cost-effectiveness was then also calculated for 50% and 25% of the original price of anastrozole, as well as for 75%, 50% and 25% of the original price of letrozole.

The incidences of adverse and severe adverse events were taken from the BIG 1-98 and ATAC studies. The costs of treatment for these events were calculated using published data or standard care as set by an expert panel. In the model, adverse side effects only occurred during treatment.

The costs of diagnosis and consequent treatment for a disease-specific event were calculated in the same way as the costs for adverse events.

Quality of Life Data

Morbidity, mortality and quality of life were included in this cost-effectiveness analysis in combined form through QALYs. To calculate QALYs, data on health utilities in the various treatment and disease settings were required. As international data may diverge considerably from those in women living in Germany, health utilities were obtained at the Department of Gynecology in the Erlangen University Hospital using a visual analog scale (VAS; scale 0–100). Health utilities were obtained and evaluated for 600 patients so that the present analysis was able to

draw on real data for women treated in Germany [17]. Table 1 shows the health utilities for the various disease situations.

When data for changes in health utilities were lacking relative to adverse and severe adverse events that occurred, with the exception of primary disease in endometrial carcinoma, published values from American and British breast carcinoma patients were used [18]. The mean age was 68 years. All patients received an endocrine therapy in the adjuvant setting, 56% had a previous radiotherapy and 16% adjuvant chemotherapy. Health status due to adverse events associated with endocrine therapy was assessed using the standard gamble technique for 67 patients (table 2). Here, the patients had to choose between 2 alternatives: gamble of living in perfect health versus immediate death, or certainty of being in the hypothetical health state being measured. Then scores were adjusted to a scale of 0–1.0.

Sensitivity Analysis

Sensitivity analyses were carried out to test the uncertainty of the data entered into the model. Simple standard deviation was used for cost parameters, and published confidence intervals were used for clinical efficacy parameters. Probability calculation was carried out using a Monte Carlo simulation with 2000 scenarios. The validity of the model is presented using cost effectiveness-acceptance curves, which present the probabilities of the various incremental cost-effectiveness ratios (ICERs).

Results

Parameters in the Model

The costs calculated for the endocrine treatments and for patient care, taking into account the assumed price reductions (75%, 50% and 25%), are shown in table 3.

Table 1. Health utilities in the model relative to the disease situation [17]

Disease situation	Data collection method	n	Median	Standard deviation
Disease free during follow-up with status post breast carcinoma	VAS	168	75.000	17.3169
Recurrent breast carcinoma	VAS	19	71.500	18.5663
Metastatic breast carcinoma, overall	VAS	84	70.000	20.8940
Recurrent <i>and</i> metastatic breast carcinoma	VAS	29	69.000	22.0691
Metastatic breast carcinoma, chemotherapy	VAS	25	58.000	23.3128
Metastatic breast carcinoma, endocrine therapy	VAS	27	70.000	19.0694
Primary disease endometrial carcinoma	VAS	11	60.000	13.6518

VAS = Visual analog scale.

Table 2. Health utilities in the model relative to adverse events [18]

Event	n	Mean	Standard deviation
No event	67	0.974	0.033
Weight gain, hot flushes, vaginal discharge	67	0.963	0.042
Weight gain, limb pain, hot flushes, dryness of vagina	67	0.959	0.050
Deep venous thrombosis in legs	67	0.796	0.250
Hip fracture	67	0.730	0.290

Table 3. Drug costs and treatment costs for the model (based on pharmacists' prices in 2010 (100 tablets N3)

Drug	Costs for care, including prescriptions, per 3 months, €	Price reductions assumed in the model, %	Drug costs per 3 months, €	Costs per year, €
Tamoxifen	50.83	100	20.46	285.16
		75	606.77	2582.56
		50	455.08	1975.80
		25	303.39	1369.04
		25	151.69	762.24
Anastrozole	38.87	100	603.96	2571.32
		75	452.97	1967.36
		50	301.98	1363.40
		25	150.99	759.44
		25	150.99	759.44

Cost type	Period	Costs per year, €	Reference
No events (follow-up care without any findings)	years 1–3 years 4 and 5 year 1	360.92 227.40 15,044.01	[19]
Recurrences	years 2 and 3 years 4 and 5 year 1	574.79 441.27 18,361.62	[19, 20]
Contralateral breast carcinoma	years 2 and 3 years 4 and 5 year 1	574.79 441.27 19,514.27	[19]
Metastases	year 1	19,514.27	[21]
Terminal care	last 4 weeks	7472.39	[19]

Table 4. Costs for follow-up care and disease-specific events

Adverse/severe adverse event	Period	Costs, €	Reference
Transitory ischemic attack (TIA)	first 3 months from event	3078.48	[16, 22]
Thromboembolism	first 3 months from event	2463.39	[16, 23]
Vaginal bleeding	per event	1319.72	[14, 23]
Arthralgia	per month	27.04	[14, 16]
Myalgia	per month	27.04	[14, 16]
Endometrial carcinoma	per event	6879.52	[14, 23]
	follow-up care, per visit	89.94	
	overall follow-up care	1439.04	
	overall costs	8318.56	
Bone fracture, without surgery	per event	2074.22	[16, 23]
Bone fracture, with surgery (with femoral fracture as example)	per event	5340.79	[14, 16]

Table 5. Costs of adverse and severe adverse events

In addition to direct costs for drugs, these also include the costs for diagnosis (e.g., physical examination, DXA scanning) and care (patient history, physical examination, prescriptions, etc.). The different costs for care are based on the vaginal ultrasound and examination every 6 months in case of tamoxifen.

The costs calculated for follow-up measures and for the occurrence of disease-specific events (recurrences, contralateral breast carcinoma, metastases) are shown in table 4 [19–21], and the costs calculated for adverse events and severe adverse events for each type of endocrine therapy are shown in table 5 [14, 16, 22, 23].

Cost-Benefit Analysis

Using the present analysis, total costs for the basic assumption (75% price for anastrozole and 100% price for letrozole) of € 16,308.10 for adjuvant endocrine therapy with tamoxifen, € 25,484.12 for letrozole, and € 22,546.14 for anastrozole were calculated (table 6). The substantial differences from tamoxifen are due in particular to differences in direct treatment costs of € 9934.58 for letrozole and € 7351.45 for anastrozole, and the difference here is explained by the expiry of the patent for anastrozole, with an assumed price for the generic drug equivalent to 75% of the original price. With regard to efficacy, gains of 0.3090 life-years for letrozole and 0.0440 life-years for anastrozole were calculated in comparison with tamoxifen. With regard to costs, incremental costs of €29,691.85 per life-year for letrozole (100% price) in comparison with tamoxifen and € 141,673.73 per life-year for anastrozole (75% price) in comparison with tamoxifen were calculated (table 6). In addition, the cost-benefit model based on survival, taking into account the health utilities obtained in

Germany, shows gains of 0.3124 and 0.0659 QALYs for letrozole and anastrozole, respectively, in comparison with 5 years of treatment with tamoxifen.

With regard to costs, incremental costs of € 29,375.15 per QALY (95% confidence interval (CI), € 17,323–122,339) for letrozole (100% price) in comparison with tamoxifen and € 94,648.03 per QALY (95% CI, € 25,997–1,010,381) for anastrozole (75% price) in comparison with tamoxifen were calculated (table 6).

The cost-effectiveness improves markedly with a further reduction in the price of anastrozole; at 50% of the original price, the figure would be € 54,715.17 per QALY, and at 25% of the price, it would be € 14,779.67 per QALY.

By contrast, the cost-effectiveness after a price reduction with letrozole continues to favor letrozole. With a price reduction after expiry of the patent to 75% of the original price, the cost-effectiveness would be € 20,988.59 per QALY; at 50%, it would be € 12,602.03 per QALY, and at 25% of the price it would be € 4215.46 per QALY (table 6).

Sensitivity Analysis

The probability of cost-effectiveness with the basic assumption for letrozole (100%) versus anastrozole (75%) is illustrated in figure 1. The resulting probability curves for cost-effectiveness in comparison with tamoxifen for the various prices are shown in figures 2 and 3.

Moreover, the scatter plot of the basic assumption scenario (75% price for anastrozole and 100% price for letrozole) is presented in figure 4. This cost-effectiveness plane represents the cost and QALY differences for each of the separate runs that are undertaken as part of the probabilistic sensitivity analysis. The chart shows that letrozole is always more costly,

Table 6. Results of the model

	Tamoxifen	Letrozole					Anastrozole				
		100%	75%	50%	25%		100%	75%	50%	25%	
Treatment costs	€ 1218.79	€ 11,153.37	€ 8533.63	€ 5913.89	€ 3294.15		€ 11,202.12	€ 8570.24	€ 5938.35	€ 3306.30	
Costs for DFS	€ 4024.41	€ 4229.81	€ 4229.81	€ 4229.81	€ 4229.81		€ 4146.42	€ 4146.42	€ 4146.42	€ 4146.42	
Costs for disease-specific events	€ 10,528.57	€ 9491.92	€ 9491.92	€ 9491.92	€ 9491.92		€ 9254.17	€ 9254.17	€ 9254.17	€ 9254.17	
Costs of AEs/SAEs	€ 536.33	€ 609.02	€ 609.02	€ 609.02	€ 609.02		€ 575.31	€ 575.31	€ 575.31	€ 575.31	
Overall costs	€ 16,308.10	€ 25,484.12	€ 22,864.38	€ 20,244.64	€ 17,624.90		€ 25,178.02	€ 22,546.14	€ 19,914.25	€ 17,282.20	
Life-year	12.4860	12.7950	12.7950	12.7950	12.7950		12.5300	12.5300	12.5300	12.5300	
QALYs	11.7267	12.0391	12.0391	12.0391	12.0391		11.7926	11.7926	11.7926	11.7926	
Incremental costs per life-year compared with tamoxifen	–	€ 29,691.85	€ 21,214.87	€ 12,737.89	€ 4260.91		€ 201,447.16	€ 141,673.73	€ 81,900.30	€ 22,122.93	
Incremental costs per QALY compared with tamoxifen	–	€ 29,375.15	€ 20,988.59	€ 12,602.03	€ 4215.46		€ 134,580.89	€ 94,648.03	€ 54,715.17	€ 14,779.67	
ICER, 95% CI	–	€ 17,323–122,339	€ 11,942–79,981	€ 6871–56,002	€ 1327–16,623		€ 37,912–1,365,392	€ 25,997–1,010,381	€ 14,188–496,141	€ 1389–203,147	

AE = Adverse event, DFS = disease-free survival, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, SAE = severe adverse event.

Fig. 1. Cost-effectiveness curve for the initial model for anastrozole (red) at 75% of the original price versus letrozole (blue) at 100% of the original price.

but it is also always more effective than tamoxifen, whereas anastrozole has a fair probability of being less effective than tamoxifen.

Discussion

Numerous studies have been published in recent years on the use of AIs in the adjuvant setting, but none of these has taken the potential generic prices for the agents into account. A total of 20 publications were evaluated in a recent meta-analysis (8 on anastrozole, 8 on letrozole, and 4 on exemestane) [24]. Median ICERs of \$ 21,113 for letrozole, \$ 21,428 for exemestane, and \$ 24,932 for anastrozole were found. As all of the values were below the accepted threshold value of \$ 25,000, the authors concluded that administration of AIs is always a cost-effective option in comparison with tamoxifen.

Another published meta-analysis of the available economic analyses of the 3 AIs in comparison with tamoxifen was carried out by the Health Technology Assessment (HTA) program in 2007 to provide data for decisions taken by the National Institute for Health and Clinical Excellence (NICE) [25]. The AIs were evaluated as a cost-effective form of treatment. However, it was emphasized, qualifying this, that further research results are needed to confirm the usual extrapolation of the benefits in terms of disease-free survival and recurrence-free survival to the overall survival as well. These data are now available.

In the 100-month data for the ATAC study, a significantly longer disease-free survival (HR 0.85; 95% CI 0.76–0.94; $p = 0.003$) and a significantly longer period to recurrence (HR 0.76; 95% CI 0.67–0.87; $p = 0.0001$) was observed for anastrozole in comparison with tamoxifen [11]. Although fewer deaths occurred in the anastrozole arm (472 versus 477), the overall survival was not significantly longer (HR 0.97; 95% CI 0.86–1.11; $p = 0.7$). In the BIG 1-98 study, an

Fig. 2. Cost-effectiveness curve for letrozole (red) at (a) 100%, (b) 75%, (c) 50%, and (d) 25% of the original price versus tamoxifen (blue).

intention-to-treat (ITT) analysis of the 2 single-treatment arms (5 years of letrozole versus 5 years of tamoxifen) after a median follow-up period of 76 months showed a significant advantage for letrozole, both in relation to recurrence-free survival (HR 0.88; 95% CI 0.79–0.99) and also distant metastasis-free survival (HR 0.85; 95% CI 0.7–1.00). With regard to the overall survival, the ITT analysis showed a trend in favor of the AI (HR 0.87; 95% CI 0.7–1.02) [9]. The problem with these data is that, due to the better effectiveness that was emerging for letrozole, unblinding of the study was carried out for ethical reasons, as a result of which 25% of the women switched to the letrozole arm. This selective cross-over made subsequent analysis more difficult, as these women continued to be assigned to the control arm in the ITT analysis, reducing the potential difference between the 2 treatment arms. This led to a censored analysis, in which a significant difference was found in the overall survival (HR 0.81; 95% CI 0.69–0.94) (fig. 4) [10]. To compensate for underestimation in the ITT analysis and overestimation in the censored analysis, an IPCW analysis of the BIG 1-98 study was published [10], which provides an opportunity to see how the study might have fared without selective cross-over. It was shown once

again that letrozole significantly improved the overall survival by 17% in comparison with tamoxifen (HR 0.83; 95% CI 0.71–0.97; $p < 0.05$) [10]. As expected, the results were intermediate between the figures for the ITT and censored analyses.

The present cost-benefit analysis incorporates the survival data mentioned above; taking into account expected price reductions due to the expiry of the patent for anastrozole to 75%, 50% and 25% of the original price and the future expiry of the patent for letrozole, with the same estimated price reductions, the study compares the cost-benefit values for letrozole and anastrozole with tamoxifen in postmenopausal patients with hormone-receptive breast carcinoma. For the basic assumption with letrozole (100% of the price), the cost-benefit figure is € 29,375.15 per QALY. This is also the first cost-benefit analysis for letrozole in comparison with tamoxifen in the context of the German health care system that takes health utilities in Germany into account.

Comparable international data are available [26, 27]. Delea et al. [26] investigated the cost-benefit ratio for letrozole in comparison with tamoxifen on the basis of the American health care system and data from the BIG 1-98 study, assuming a carry-over effect of 5 years. A gain of 0.409 QALYs in

Fig. 3. Cost-effectiveness curve for anastrozole (red) at (a) 100%, (b) 75%, (c) 50%, and (d) 25% of the original price versus tamoxifen (blue).

comparison with tamoxifen and additional costs of \$ 9705 with letrozole treatment were observed. This led to costs of \$ 23,743 per QALY (95% CI, \$ 14,087–51,129).

Numerous published cost-benefit analyses are also available for anastrozole in comparison with tamoxifen, although most of these are based on the 60-month data from the ATAC study [28–33]. Karnon [32] previously carried out a meta-analysis of the published data for the AIs, showing that anastrozole is cost effective. An analysis from the point of view of the American health care system estimated an ICER of \$ 20,246 per QALY for anastrozole in comparison with tamoxifen [31].

By contrast, the present analysis shows a cost-benefit value of € 94,648.03 (95% CI, € 25,997–1,010,381) for up-front therapy with anastrozole at 75% of the original price in comparison with treatment with tamoxifen. At 100% of the original price, the figure would be as high as € 134,580.89 per QALY (table 6). This result clearly diverges from the previously published data, including those reported in a study based on the health care system in Germany [34]. Using the ATAC 100-month data, the latter study indicated costs of € 21,069 per QALY gained (95% CI, € 12,567–46,604). The

Fig. 4. Scatter plot of the basic assumption scenario (75% price for anastrozole and 100% price for letrozole – cost and QALY differences).

differences are based on the problem that the ATAC study did not show a significant benefit in relation to overall survival, but only for disease-free survival. However, numerous cost-benefit analyses for AIs have extrapolated the disease-

free survival to the overall survival. This procedure is a matter of controversy [35, 36]. But Cuzick argues in his paper that disease-free survival is a widely accepted end point in numerous clinical studies [35], so that overall survival in a group with an initially good prognosis cannot be used, as the patients die due to other diseases and the overall survival resulting from a therapeutic innovation is no longer measurable. In the publication by Lux et al. [34] mentioned above, a longer overall survival was estimated on the basis of a significantly prolonged time to recurrence due to treatment with anastrozole. Although this assumption is accepted from the health economics point of view, it was dispensed with in the present analysis, and the pure published survival data from the studies were used without extrapolation in order to avoid additional uncertainties in the model.

A comparable analysis using IPCW data from the BIG 1-98 study in comparison with data from the ATAC study has also been published [37]. Over a period of 20 years, the discounted additional treatment costs for letrozole were $\leq$ £ 3618. Taking all adverse side effects and avoidance of recurrences into account, the cost difference from tamoxifen was $\leq$ £ 2964. With a gain of 0.297 QALYs, an ICER of $\leq$ £ 9999 for letrozole was estimated. For anastrozole, this value was $\leq$ £ 48,829. The authors concluded that letrozole is a substantially better strategy in comparison with anastrozole. These data from England confirm both the present results from the German study and also the validity of the model based on survival data.

Although the results of this work are confirmed by several international studies, some limitations have to be mentioned. The results are based on a model. The validation with real data would be helpful and should be part of health services research. Moreover, the model is based on the IPCW analysis, which can only weight known patient characteristics and tumor parameters. An adjustment of unknown prognostic factors is not possible.

One further statistical limitation is the fact that the mortality tables for the 76–80-year-old women are based on the general population. A bias is possible, because mortality rates 15–20 years post early breast cancer will be low compared to all-cause mortality rates. This may slightly underestimate mortality. Increasing the mortality probabilities in this age group to 5% increases the ICER of letrozole by € 200; so the effect on the cost-effectiveness would be marginal.

Last but not least, compliance has to be mentioned, which could influence the results of the model. It is known that compliance in real life is different to clinical trials. This is especially relevant for endocrine therapies regarding the long duration of intake (at least 5 years, up to 10 years possible) and the side effects. Non-adherence and non-persistence due to non-compliance can decrease overall survival (HR = 1.26 and HR = 1.49) [38]. Moreover, it can cause costs by additional relapses and metastasis, which need cost-intensive therapies. On the other side, results of cost-effectiveness models can have a positive influence on the perception of endocrine therapies and optimize compliance.

Conclusions

The present model – taking into account the current state of data with an IPCW analysis for letrozole and also the current expiry of the patent for anastrozole and the impending expiry of the patent for letrozole – shows that letrozole is cost effective in postmenopausal patients with hormone receptor-positive breast carcinoma. The new Drug Market Reform Law of November 2010 introduced rapid evaluation of new drugs to demonstrate additional benefit in Germany. Although the German model was based on the Scottish Medicines Consortium (SCM) method of assessing new drugs, there are clear differences. Whereas a cost-benefit assessment is carried out in Scotland and a threshold value of € 30,000/QALY is set for a positive judgement of benefit, in Germany only the benefit is assessed, without a threshold value. However, the present analysis does also meet the criteria for cost-effectiveness using the Scottish threshold value.

It is also the first cost-benefit analysis for letrozole in comparison with tamoxifen to be conducted in the context of the German health care system, taking into account health utilities in Germany, potential price reductions for both drugs, and current survival data.

Disclosure Statement

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