Breast Care

Original Article · Originalarbeit

Breast Care 2009;4:389–396
DOI: 10.1159/000255840

Published online: December 11, 2009

Cost Effectiveness of Exemestane versus Tamoxifen in Post-Menopausal Women with Early Breast Cancer in Germany

Sebastian Braun[a] Thomas Mittendorf[a] Thomas Menschik[b] Wolfgang Greiner[c] Johann-Matthias von der Schulenburg[a]

[a] Centre for Health Economics, Leibniz University of Hanover, Germany
[b] European Department of Oncology, Pfizer, Paris, France
[c] Health Economics and Health Care Management, University of Bielefeld, Germany

Key Words
Aromatase inhibitors · Postmenopause · Cost effectiveness · Breast cancer · Early stage

Summary
Background: Medical studies have shown that switching to exemestane after 2–3 years of adjuvant treatment with tamoxifen is effective when looking at overall survival. No cost effectiveness study of exemestane has been conducted in the German health care context. **Patients and Methods:** To assess the cost effectiveness of switching to exemestane vs. continued tamoxifen therapy for early-stage breast cancer, a Markov model was developed. The model population was set as postmenopausal women who are in remission from early-stage breast cancer. Upon model entry, either a continuing daily therapy with 20 mg tamoxifen or a switch to 25 mg exemestane for the next 2–3 years takes place. The model takes a German health care perspective. **Results:** The total incremental costs of exemestane on a lifetime basis are 4,195 Euro, resulting in an incremental cost effectiveness ratio of 17,632 Euro per additional quality-adjusted life year (QALY), or 16,857 Euro per life year gained. Incremental costs per disease-free year of survival are 12,851 Euro. Probabilistic sensitivity analyses proved the robustness of these findings. **Conclusion:** Compared to extended tamoxifen therapy, switching to exemestane after 2–3 years turned out to be a cost-effective strategy in adjuvant therapy for early-stage breast cancer in postmenopausal women within the German health care context.

Schlüsselwörter
Aromatasehemmer · Postmenopause · Kosteneffektivität · Brustkrebs · Frühstadium

Zusammenfassung
Hintergrund: Klinische Studien belegen, dass der Wechsel zu Exemestan nach 2–3 Jahren adjuvanter Tamoxifentherapie die Gesamtüberlebenszeit verlängern kann. Bisher existieren für den deutschen Versorgungszusammenhang keine Studien zur Kosteneffektivität dieses Therapieschemas. **Patienten und Methoden:** Anhand eines Markov-Modells wird die Kosteneffektivität des Wechsels zu Exemestan mit der Fortführung der Tamoxifentherapie verglichen. Die Zielpopulation sind postmenopausale Frauen mit Brustkrebs in Remission, die vor Modelleintritt 2–3 Jahre lang Tamoxifen erhalten haben. Die tägliche Therapie wird entweder mit 20 mg Tamoxifen oder mit 25 mg Exemestan für weitere 2–3 Jahre fortgesetzt. Das Modell verwendet die Perspektive des deutschen Gesundheitswesens. **Ergebnisse:** Die inkrementellen Gesamtkosten von Exemestan betragen bei lebenslanger Betrachtung 4195 Euro. Die Kosteneffektivität liegt bei 17 632 Euro pro zusätzlichem qualitätsangepasstem Lebensjahr (QALY) bzw. 16 857 Euro pro gewonnenem Lebensjahr und 12 851 Euro für ein zusätzliches krankheitsfreies Jahr. Probabilistische Sensitivitätsanalysen bestätigen die Stabilität dieser Ergebnisse. **Schlussfolgerung:** Verglichen mit der verlängerten Tamoxifentherapie ist der Wechsel zu Exemestan nach 2–3 Jahren kosteneffektiv in der adjuvanten Brustkrebstherapie bei postmenopausalen Frauen innerhalb des deutschen Gesundheitswesens.

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Dipl.-Ök. Sebastian Braun
Leibniz Universität Hannover
Forschungsstelle für Gesundheitsökonomie
Königsworther Platz 1, 30167 Hannover, Germany
Tel. +49 511 762-5518, Fax -5081
sbr@ivbl.uni-hannover.de

Introduction

For more than 30 years, the standard approach to adjuvant treatment of oestrogen receptor-positive early-stage breast cancer in postmenopausal women was to treat patients with up to 5 years of tamoxifen. Tamoxifen has been shown to be very effective and to reduce breast cancer-related mortality by up to 50% [1]. With the third-generation aromatase inhibitors, an even more effective substance class was introduced as therapeutic alternative [2–7]. Hence, international guidelines state that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer should include an aromatase inhibitor, either as initial therapy or after treatment with tamoxifen [8]. Also German guidelines acknowledge the superiority of third-generation aromatase inhibitors compared to tamoxifen for assured postmenopausal woman with early-stage breast cancer [9]. One of the possible treatment strategies emerging from these guidelines and advances in daily clinical practice is to initially treat patients with tamoxifen for the first 2–3 years and then to switch to alternative treatments such as exemestane. The objective of this model is to assess the costs and health outcomes of continuing to use adjuvant tamoxifen therapy for a further 2–3 years compared with switching to adjuvant treatment with exemestane at 2–3 years, in the German health care context.

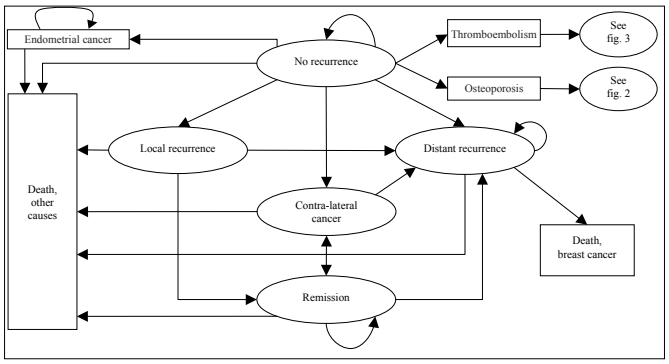

Fig. 1. General structure of the Markov model.

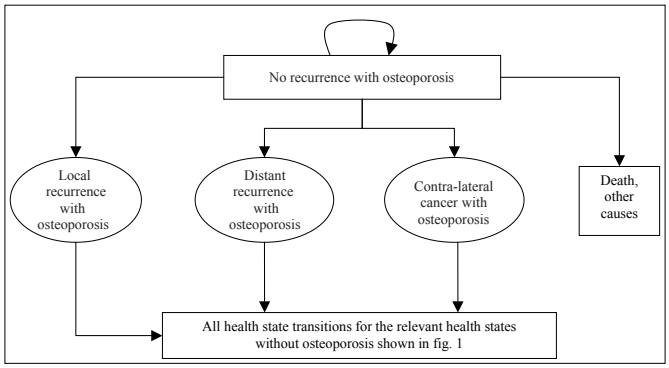

Fig. 2. Allowable transitions in the case of osteoporosis.

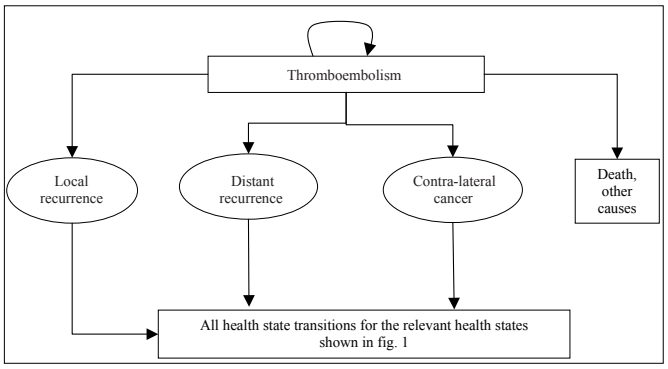

Fig. 3. Allowable transitions in the case of thromboembolism.

Patients and Methods

A Markov model was developed in Microsoft Excel® to assess the cost effectiveness of exemestane relative to continued tamoxifen as adjuvant therapy for early-stage breast cancer. Cost and health outcomes were assessed in terms of the incremental cost per life year gained, the incremental cost per quality-adjusted life year (QALY) gained, or the incremental cost per disease-free life year gained. The latter outcome demonstrates the treatment impact on surrogate markers that determine whether treatment is a success or a failure.

Model Structure

This model takes the perspective of the German Statutory Health Insurance (SHI). It is difficult to collect data showing the productivity loss associated with early-stage breast cancer or its treatment. A true measurement is likely to show that such costs are relatively small, due to the age of the population. The model therefore only considers health care-related costs.

The model uses the following health states to demonstrate differences between the different treatment arms in the model:

– no recurrence of breast cancer
– remission from breast cancer
– local recurrence of breast cancer
– distant recurrence of breast cancer
– contra-lateral breast cancer
– death from breast cancer
– death from other causes

Osteoporosis, endometrial cancer and thromboembolism (pulmonary embolism (PE) and deep-vein thrombosis (DVT)) are incorporated into the model as adverse events using separate health states. Osteoporosis is included by replicating all of the health states listed above (osteoporosis with no recurrence, osteoporosis with disease remission, osteoporosis with local recurrence, osteoporosis with distant recurrence, osteoporosis with contra-lateral breast cancer). Once a patient is diagnosed with osteoporosis, she stays in an osteoporosis-related state but can still transition between different health states in the same way as patients without osteoporosis.

Endometrial cancer is incorporated in a manner different to osteoporosis. It is assumed that endometrial cancer 'dominates' other states in the model, so that patients can only remain in the endometrial cancer health state or move to death. This assumption is based on discussions with clinical experts. Thromboembolism is included as a reversible event with a separate health state. Patients are able to move to breast cancer-related health states once the thromboembolism has resolved.

Table 1. Health state and adverse event utilities

Health state	Utility value	Source
No recurrence	0.999	Carter et al. (1998) [13]
Local recurrence	0.700	Desch et al. (1993) [14]
Remission after local recurrence	0.850	Hillner et al. (1991) [15]
Distant recurrence	0.517	Karnon et al. (2004) [16]
Contra-lateral disease	0.700	assumed as being the same as local recurrence
Osteoporosis	0.930	Kanis et al. (2005) [17]
Osteoporotic fracture	0.860	assumption – midpoint between hip (0.79) and no fracture (0.93); Kanis et al. (2005) [17]
Endometrial cancer	0.740	Ozanne et al. (2004) [18]
Thromboembolism	0.580	Eckman et al. (1993) [19]
Thromboembolism post treatment	0.900	Cykert et al. (2004) [20]
Death	0.000	

Table 2. Transition probabilities used in the first 36 months of the model

Probability	Exemestane	Tamoxifen	Discontinued
From no recurrence to			
Contra-lateral breast cancer	0.000536	0.001674	0.003193
Contra-lateral breast cancer (end of treatment)	0.001776	0.001776	na
Distant recurrence	0.012022	0.015596	0.016908
Distant recurrence (end of treatment)	0.011455	0.011455	na
Local recurrence	0.002765	0.004104	0.005542
Local recurrence (end of treatment)	0.002564	0.002564	na
Remaining in no recurrence	residual	residual	residual
Death from other causes	age-dependent German mortality data [11]		
From disease remission to			
Distant recurrence	0.051395	0.051395	na
Remaining in disease remission	residual	residual	na
Death from other causes	age-dependent German mortality data		
From local recurrence to			
Distant recurrence	0.051395	0.051395	na
Disease remission	residual	residual	na
Death from other causes	age-dependent German mortality data [11]		
From distant recurrence to			
Remaining in distant recurrence (survival)	0.179665	0.179665	na
Death from other causes	age-dependent German mortality data [11]		
Death from breast cancer	residual	residual	residual
From contra-lateral breast cancer to			
Distant recurrence	0.051395	0.051395	na
Remission to distant recurrence	residual	residual	na
Death from other causes	German age-specific mortality data [11]		

na = Not applicable.

Other adverse events are also included in the model. The impacts of vaginal haemorrhage, cardiac failure, myocardial ischaemia, arthralgia, and hypertension on health care costs are incorporated into the model as event tolls. These events were deemed either too rare to justify a separate health state, or clinical advice stated that the impact on quality of life was likely to be minimal. The general structure of the model and its allowable transitions are displayed in figure 1.

Allowable transitions from two adverse events – osteoporosis and thromboembolism – are shown in the separate diagrams of figures 2 and 3. Osteoporosis is a permanent condition in the model, but one that operates independently of breast cancer. That is, a patient with osteoporosis will have osteoporosis for the rest of her life, but the breast cancer will progress at the same rate as if a patient did not have osteoporosis.

Thromboembolism is also incorporated into the model. It is assumed that the episode is successfully treated, after which patients either remain in the post-thrombolytic state (equivalent to no recurrence) or transition to one of the other states that those in the no-recurrence health state are able to move to (as shown in fig. 1).

The population included in the model reflects the study data of the Intergroup Exemestane Study (IES) [10]. Hence, the cohort in the model consists of postmenopausal women with a median age of 63 years (range 31–96 years) who had already spent an average 28.5 months (range 15.6–

63 months) on tamoxifen before either switching to exemestane or remaining on tamoxifen. Therefore, patients who enter the model are in remission and are treated with either 20 mg tamoxifen or 25 mg exemestane daily. After this point, adjuvant treatment is stopped, although patients receive other treatments if disease progresses or if adverse events occur.

The time horizon for the cohort was lifetime (maximum 38 years from a starting age of 63). German age-specific mortality data [11] were used to incorporate death from other causes. Finally, a cycle length of 6 months was chosen for the model as reasonable assumption for the time taken to transition between the health states according to clinical experts. A half-cycle correction was employed to take into account the fact that events occur during the cycle period and not only at the end of a cycle.

The model calculates the average cost and outcome on a per patient basis. With this, incremental cost effectiveness ratios can be calculated. The average costs per treatment arm over the duration of the model are calculated as the sum of the cycle costs on each arm. Costs and outcomes occurring after the first year are discounted with 5% per annum, as recommended by the third and updated version of the Hanover Consensus, which is the current guideline for health economic evaluation in Germany [12].

Clinical Data

The utilities attached to the different health states and adverse events used in the model are shown in table 1. International data had to be incorporated as no German-specific utilities were available for this context. The model also includes a probabilistic sensitivity analysis. In this way, the impact of variation due to uncertainty around the key parameters (transition probabilities, costs and utilities) on the baseline cost effectiveness results can be assessed. Probabilistic cost effectiveness results are obtained using 1000 Monte Carlo simulations.

The transition probabilities used in the first 36 months of the model are displayed in table 2. These transition probabilities are taken from the results of the IES trial and represent the probability of moving from one health state to another. However, it is important to consider the probabilities used beyond the 36-month follow-up of the pivotal trial. In order to be conservative, it was assumed that exemestane and tamoxifen would have the same effect in preventing recurrences after the end of the follow-up period, despite the fact that exemestane patients showed fewer recurrences over the 36-month follow-up period. This is a conservative assumption that will increase the value of the incremental cost effectiveness ratio.

The data used to estimate the transition probabilities after the end of the trial follow-up were based on three key publications. First, the probabilities of progressing from no recurrence to local recurrence, distant recurrence and contra-lateral disease were based on 15-year survival data for tamoxifen [1]. Firstly, this data tracks the progression of breast cancer patients over time and provides a strong source for estimating transition probabilities that are needed over the long time period. Secondly, the probability of remaining in the distant-recurrence health state is derived from a key observational study [21]. These results showed that median survival is 21 months among metastatic breast cancer patients, tracking the survival of metastatic breast cancer patients over the medium term. A third key source was used to estimate the probability of progressing from local recurrence to distant recurrence [22]. The results of that study showed that 41% of the patients progressed from local breast cancer to distant-stage breast cancer over a 5-year period. Overall, 6-month probabilities for each of these transitions were calculated based on these results.

Resource Use and Unit Costs

The model parameters were mainly identified on the basis of the DRG Browser [23] for inpatient costs, the EBM 2000 plus [24] (official remuneration within the SHI for outpatient services), and current market prices for drugs [25]. With the assistance of medical experts, the appropriate diagnosis-related groups (DRGs) were identified. For calculation of the DRG-based costs, we assumed a base case value of 2831 Euro. The costs according to the EBM were calculated with a calculatory point score of 0.051 Euro.

For drugs, market prices for the SHI as recorded in the Red Book were applied, always using the largest available package size. If a com-

Table 3. Cost parameters

Model parameters	Costs	Source
Tamoxifen 20 mg	54.31 €	Red Book [25]
Exemestan 25 mg	1005.34 €	Red Book [25]
Osteoporosis		
Osteoporosis pharmaceuticals	210.12 €	Red Book [25]
Osteoporosis fracture	2878.72 €	DRG Browser V2005 [23]
Thromboembolism		
Costs of the initial episode	3239.66 €	DRG Browser V2005 [23]
Running costs for the first model cycle after incidence	93.28 €	EBM 2000 plus [24], Red Book [25]
Following cycles up to 3 years after incidence	62.47 €	EBM 2000 plus [24], Red Book [25]
Endometrial cancer		
Diagnosis (once)	21.42 €	EBM 2000 plus [24]
Operation (with radiotherapy) (once)	5692.97 €	DRG Browser V2005 [23]
Chemotherapy (1. regime)	3201.36 €	Red Book [25]
Breast cancer therapy		
Operation cost (either breast ablation or preservation) (once)	4188.12 €	DRG Browser V2005 [23]
Chemotherapy (1. regime responders)	3201.36 €	Red Book [25]
Chemotherapy (1. regime non-responders/3 months of treatment)	1600.68 €	Red Book [25]
Chemotherapy (2. regime)	11,053.95 €	Red Book [25]
Terminal care		
Medical home care or nursing home (14 days)	460.53 €	EBM 2000 plus [24]
At hospital or hospice (14 days)	3609.53 €	DRG Browser V2005 [23]
Weighted average costs	2223.97 €	

Table 3. Continued

Model parameters	Costs	Source
Routine care if well (5 years of treatment)		
Home visit by the doctor (twice per year with 20.40 € each)	204.00 €	EBM 2000 plus [24]
GP visit (4 × per year with 11.48 € each)	229.50 €	EBM 2000 plus [24]
Cardiac failure		
GP visit	11.48 €	EBM 2000 plus [24]
Cardiology outpatients	75.74 €	EBM 2000 plus [24]
ECG	0.00 €	EBM 2000 plus [24]
Mammogram	36.72 €	EBM 2000 plus [24]
Phlebotomy	0.00 €	EBM 2000 plus [24]
Biochemistry	7.20 €	EBM 2000 plus [24]
Haematology	1.10 €	EBM 2000 plus [24]
Spirometry	57.12 €	EBM 2000 plus [24]
ECHO	0.00 €	EBM 2000 plus [24]
Frusemide	25.58 €	Red Book [25]
Carvedolol	217.94 €	Red Book [25]
Enalapril	44.64 €	Red Book [25]
Lisinopril	42.86 €	Red Book [25]
Influenza vaccine	24.07 €	Red Book [25]; own calculation
Pneumococcal vaccine (once)	41.97 €	Red Book [25]; own calculation
Total cost of cardiac failure	421.65 €	
Hypertension		
GP visit	22.95 €	EBM 2000 plus [24]
Bendrofluazide 2.5 mg	51.14 €	Red Book [25]
Enalapril	44.64 €	Red Book [25]
Lisinopril	42.86 €	Red Book [25]
Atenolol	34.07 €	Red Book [25]
Amlodipine	37.57 €	Red Book [25]
Nifedipine XL	43.09 €	Red Book [25]
Losartan	178.35 €	Red Book [25]
Valsartan	77.30 €	Red Book [25]
Total cost of hypertension	151.38 €	Red Book [25]
Arthralgia		
GP visit	11.48 €	EBM 2000 plus [24]
Paracetamol	82.22 €	Red Book [25]
Naproxen	56.56 €	Red Book [25]
Diclofenac	26.57 €	Red Book [25]
Total cost of arthralgia	66.66 €	
Vaginal haemorrhage		
Hysteroscopy und biopsy	683.40 €	KBV EBM 2000 plus
Ultrasound	19.38 €	KBV EBM 2000 plus
Histology	26.27 €	KBV EBM 2000 plus
Total cost of vaginal haemorrhage	729.05 €	
Myocardial ischaemia		
GP visit	11.48 €	EBM 2000 plus [24]
Outpatient visit cardiology	75.74 €	EBM 2000 plus [24]
ECG	0.00 €	EBM 2000 plus [24]
Phlebotomy	0.00 €	EBM 2000 plus [24]
Biochemistry	7.20 €	EBM 2000 plus [24]
Exercise tolerance test	27.80 €	EBM 2000 plus [24]
GTN spray	63.72 €	Red Book [25]
Atenolol	34.07 €	Red Book [25]
Isosorbide mononitrate	21.40 €	Red Book [25]
Total cost of myocardial ischaemia	248.40 €	

ECG = Electrocardiogram, ECHO = echocardiography, GTN = glyceryl trinitrate.

Table 4. Time spent in each health state

Health state	Time spent in each health state, years	
	Exemestane	Tamoxifen
No recurrence	12.124	12.309
No recurrence with osteoporosis	2.243	1.343
Total time in no recurrence	14.367	13.652
Local recurrence	0.032	0.037
Local recurrence with osteoporosis	0.006	0.004
Total time in local recurrence	0.038	0.041
Contra-lateral disease	0.020	0.024
Contra-lateral disease with osteoporosis	0.004	0.002
Total time in contra-lateral disease	0.024	0.026
Distant recurrence	0.217	0.240
Distant recurrence with osteoporosis	0.039	0.025
Total time in distant recurrence	0.256	0.265
Remission	0.616	0.728
Remission with osteoporosis	0.112	0.073
Total time in remission	0.728	0.801
Endometrial cancer	0.025	0.036
Post-thromboembolism	0.152	0.355
Death	22.413	22.838

Table 5. Base case results

	Exemestane	Tamoxifen	Incremental
Costs	10,827 €	6,631 €	4,195 €
QALY	9.9976	9.7597	0.2379
Life years	10.2656	10.0167	0.2489
Disease-free years	9.6554	9.3289	0.3265
Incremental cost per QALY			17,632 €
Incremental cost per life year gained			16,857 €
Incremental cost per disease-free survival year gained			12,851 €

pound was not included in the fixed-price catalogue, the price of the cheapest product was taken (table 3).

The costs for an osteoporosis fracture are calculated with a weighted average based on the real-life frequency of the relevant DRGs. A thromboembolism is divided into several episodes. The costs of the first episode are divided depending on the local occurrence of embolism in the body. In this context PE and DVT are relevant, which by assumption occur at 50% each. Costs for maintenance therapy within the first model cycle after occurrence include 12 general practitioner (GP) visits, 12 blood tests and a daily dosage of 5 mg warfarin. In the following cycles of up to 3 years, the number of GP visits and blood tests is reduced to 3 each and the warfarin medication remains stable. Costs for diagnosing an endometrium carcinoma were assessed accordingly, with 3201 Euro making up for the first 6 months of chemotherapy.

Inpatient costs for treating breast cancer do also result from a weighted DRG average adding the same costs for chemotherapy as mentioned above. In non-responders, the therapy stops after 3 months. Hence, for non-responders 6-month cycle costs are half for chemotherapy. Direct medical costs for 14 days of terminal care result from home care or nursing home stays (44%) and inpatient or hospice stays (56%), respectively. The costs for routine care are the result of 2 home visits as well as 4 GP outpatient visits per year.

Finally, the costs for the 5 included therapy-related adverse events (cardiac failure, hypertension, athralgia, vaginal haemorrhage, myocardial ischaemia) were calculated as described for the other events, with physician services being based on the EBM and costs for drugs taken from the Red Book.

Results

The time spent in each health state is displayed in table 4. These results indicate that, over the model period, exemestane patients spend 0.71 more years in a no-recurrence health state than tamoxifen patients (although much of this is spent with osteoporosis). On the other hand, tamoxifen patients spend more time in local and distant recurrence, remission following recurrence, discontinuation of treatment due to an adverse event, and death. As tamoxifen patients spend more time in health states with poorer quality of life, this is likely to lead to improved overall health outcomes in the exemestane arm. The baseline results for the incremental cost per QALY gained with exemestane vs. tamoxifen are shown in table 5.

The incremental cost per QALY gained with exemestane versus tamoxifen is 17,632 Euro, suggesting that exemestane

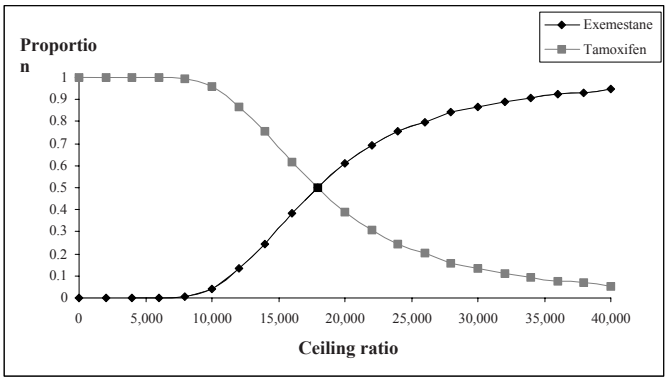

Fig. 4. Cost effectiveness acceptability curve (cost-utility).

may be a cost-effective alternative adjuvant therapy in breast cancer. As shown by the results of the disaggregated cost and outcome analyses, exemestane is only slightly more expensive than tamoxifen over the model period, and has a clear gain in health outcomes. It is these two factors that drive the cost effectiveness result.

While the incremental cost per QALY gained is generally the key result for decision makers, it is also important to measure alternatives. Life years and disease-free years are useful measures of the effectiveness of cancer treatment. Hence, baseline results for the incremental cost per life year and per disease-free year gained with exemestane versus tamoxifen are also presented in table 5.

The cost effectiveness acceptability curve (fig. 4) comes as a result of the probabilistic sensitivity analysis. It represents the likelihood that each treatment is cost effective at various willingness-to-pay thresholds. Hence, exemestane would be cost effective in over 80% of all cases at a relatively low threshold of 25,000 Euro per additional QALY.

Discussion

Up to now no evidence has been published regarding the cost effectiveness of exemestane in the German treatment setting. Hence, no comparison of the findings of this study with existing evidence is possible. However, internationally there exist three other published Markov models incorporating clinical data at least partly based on the results of the IES study [26–28]. The structures of those models as well as the findings are quite similar to the results of this modelling approach. Each study looked at the cost effectiveness in specific health care settings (Sweden and the USA), making it difficult to transfer them one by one to the German health care setting. With that in mind, the present study gives a detailed glimpse into the very specific setting of the German SHI. In future regulatory processes, the German Institute for Quality and Efficiency in Health Care (IQWiG) will play a major role by not only assessing benefits of novel treatment regimens but also looking at the cost benefit ratios. This paper could inform early discussions with such regulatory agencies in Germany, helping to optimise treatment not only from a clinical but also a health economic standpoint.

There are three main areas where our data is lacking information or can be improved:

Firstly, the clinical data input does not completely comprise the findings from clinical trials. This has led to certain assumptions in some domains being made on the basis of expert opinions. In particular, there is some missing information around each of the adverse events included in the model which could not be obtained from the literature. However, this limitation is quite common to a modelling approach like this and was addressed by conducting extensive sensitivity analyses reflecting the uncertainty around those parameters.

Secondly, there are a number of published studies that report utilities for health states equal or similar to those included in the model. Those different references could be combined in forming clinical data input into the model. However, no study could be found that included utilities for all of the health states used in the model. It would always be preferable to use as few sources as possible for the assessment of utility values, as the population used to elicit utilities has a key role in the absolute and relative utilities. Hence, the same utility values have been assigned to patients under exemestane and tamoxifen therapy, as there is no published information on differences between these two alternatives. This of course might be considered as being a more conservative as well as an optimistic reflection of treatment reality. Also, the utility values associated with recurrence of breast cancer were used as a proxy for contra-lateral breast cancer utility values, leaving a chance of under- or overestimating this estimate.

Lastly, although treatment guidelines are available for early-stage breast cancer, they are not explicit in detailing which health care pathways or regimens should exactly be used to treat those patients. Again, this has led to assumptions based on expert opinions.

Conclusion

Overall, baseline results as well as results from the probabilistic sensitivity analysis suggest that exemestane is likely to be a cost-effective alternative in comparison to tamoxifen for adjuvant therapy of early-stage breast cancer in the German health care setting.

Conflict of Interest

Preparation of this manuscript was supported by an unrestricted research grant for S.B., T.M., W.G. and J.M.S. The authors had at all times scientific freedom over the content of the publication. T.M. is a full time employee of Pfizer.

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