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Results of the Zometa® Cost-Utility Model for the German Healthcare System Based on the Results of the ABCSG-12 Study

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Key Words
Zoledronic acid · Breast cancer · Bisphosphonate · Cost-utility analysis

Summary
Background: The ABCSG-12 trial investigated the efficacy of gonadotropin-releasing hormone (GnRH)analogs in combination with tamoxifen or anastrozole ± zoledronic acid (4 mg, q6m for 3 years) in 1,803 premenopausal women with hormone receptor-positive (HR+) breast cancer. After 48 months of follow-up, there was a 36% improvement in the disease-free survival (DFS) (recurrence-free survival 35%) using zoledronic acid. Based on these data, the cost-utility of zoledronic acid was calculated for the German healthcare system. **Materials and Methods:** Costs of surveillance, adverse effects, recurrence, contralateral breast cancer, metastasis, and end-of-life care were determined based on the *Einheitlicher Bewertungsmaßstab* (EBM 2009) and the diagnosis-related groups (DRG) system. Utilities were surveyed with a questionnaire (n = 95). Estimation of the cost-utility was made by calculating the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY), using a Markov model. **Results:** Including zoledronic acid as adjuvant therapy for 3 years resulted in total costs of € 2,262. The use of zoledronic acid is dominant when clinical efficacy and quality of life are taken into consideration (–€ 45.83/QALY) (95% confidence interval (CI) –€1,838 to € 2,375; 0.02–0.41 QALY). The sensitivity analyses present with a probability of 90% that the cost per QALY gained are <€ 22,000. **Conclusion:** In the German healthcare system, zoledronic acid is a cost-effective option for premenopausal patients with HR+ breast cancer.

Schlüsselwörter
Zoledronsäure · Mammakarzinom · Bisphosphonat · Kosten-Nutzwert-Analyse

Zusammenfassung
Hintergrund: Die ABSCG-12-Studie untersuchte die Wirksamkeit von Gonadotropin-Releasing Hormon (GnRH)-Analoga in Kombination mit Tamoxifen oder Anastrozol ± Zoledronsäure (4 mg, q6m für 3 Jahre) bei 1803 prämenopausalen Frauen mit einem hormonrezeptorpositiven (HR+) Mammakarzinom. Nach einem Follow-Up von 48 Monaten zeigte sich durch Zoledronsäure eine Verbesserung des krankheitsfreien Überlebens (DFS) um 36% (rezidivfreies Überleben 35%). Basierend auf diesen Daten wurde der Kosten-Nutzwert für Zoledronsäure für das deutsche Gesundheitssystem untersucht. **Material und Methoden:** Die Kosten für Nachsorge, Nebenwirkungen, Rezidiv, kontralaterales Mammakarzinom, Metastasierung und terminale Therapie wurden erfasst. Berechnungsgrundlage waren der einheitliche Bewertungsmaßstab (EBM2009) und das diagnosebezogene Fallgruppen (DRG)-System. Utilities wurden anhand eines Fragebogens erhoben (n = 95). Die Abschätzung des Kosten-Nutzwertes erfolgte durch Berechnung der inkrementellen Kosteneffektivität (ICER, incremental cost-effectiveness ratio) pro gewonnenem QALY (quality-adjusted life year) mittels eines Markov-Modells. **Ergebnisse:** Durch Zoledronsäure für 3 Jahre in der Adjuvanz entstehen Gesamtkosten von 2262 €. Unter Berücksichtigung der klinischen Effektivität und der Lebensqualität ist der Einsatz von Zoledronsäure dominant gegenüber keinem Einsatz (–45,83 €/QALY) (95% Konfidenzintervall (CI) –1838 bis 2375 €, 0,02–0,41 QALY). Sensitivitätsanalysen zeigen, dass die Kosten pro gewonnenem QALY mit 90%iger Wahrscheinlichkeit unter 22 000 € liegen. **Schlussfolgerung:** Zoledronsäure ist im deutschen Gesundheitssystem eine kosteneffektive Therapieoption für prämenopausale Patientinnen mit einem HR+ Mammakarzinom.

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Introduction

Only a few pharmacoeconomic studies were conducted in Germany before the middle of the 1980s, since up to that time sufficient resources were available to finance the healthcare services provided [1]. Healthcare costs, however, are now rising exponentially in most countries. Recent figures show the USA at the top of the list for healthcare spending, followed by countries such as France, Switzerland, and Germany [2]. The exponential increase of costs is partly explained by the advances in medical technology and the related expansion of diagnostic and therapeutic options. Furthermore, demographic developments in industrialized countries are responsible for an increase in costs because of the care required for elderly people [3]. As a result of these developments, medical decisions must increasingly take a second dimension into account – appraisal of the costs. Available funds have to be distributed according to the necessity of services and their effectiveness (value). This calls for the requirements to be analyzed and assessed [3]. One possibility of evaluating a medical service is by using health economics decision models. The best-known model is calculation of the quality-adjusted life year (QALY) [3]. The sum of total costs is set against this index, allowing a final assessment of a new method as an effect measure (i.e. cost per QALY). In this way, measures can also be compared irrespective of indication.

In many countries, such an assessment is an integral part of the health policy. This development can also be seen in Germany. The Institute for Quality and Efficiency in Health Care (IQWiG) was founded in 2004 as a functionally independent scientific institute that is commissioned by the Federal Joint Committee to examine the benefits of health services for patients [4]. In the future, health economic analyses will be required for regulatory approval of new medicines or services, or for an extension of marketing authorization in additional indications. This also concerns products used in oncology, which are often associated with very high costs.

One example currently being discussed in healthcare policy is the use of bisphosphonates as adjuvant therapy for patients with breast cancer. Publication of efficacy data from the ABCSG-12 study by the Austrian Breast and Colorectal Cancer Study Group aroused a great deal of public interest. This study examined the clinical efficacy of an aromatase inhibitor in comparison with tamoxifen, each with and without the use of bisphosphonate therapy, in premenopausal women with hormone receptor-positive (HR+) breast cancer [5]. In the course of the 4-armed study, 1,803 premenopausal women with primary hormone-sensitive breast cancer in stages I and II were treated between 1999 and 2006. Postoperatively, the patients were given adjuvant endocrine therapy (goserelin plus tamoxifen versus goserelin plus anastrozole), with 4 mg zoledronic acid given additionally every 6 months in 2 of the arms (fig. 1). Impressive results with the additional use of the bisphosphonate were seen after a median follow-up of 47.8 months.

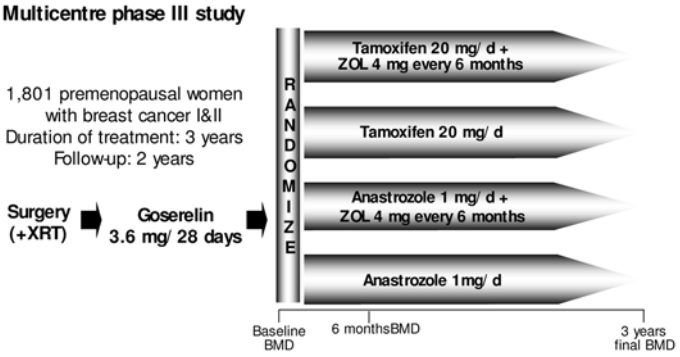


Fig. 1. ABCSG-12 study design [5].

The combination of endocrine therapy plus zoledronic acid significantly reduced the risk of a disease-free survival (DFS) event by 36% (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.46–0.91; p = 0.01) compared with endocrine therapy alone. In addition, the risk of a recurrence was reduced significantly by 35% (HR 0.65, 95% CI 0.46–0.92; p = 0.02). Owing to the short follow-up in the trial, no significant difference in overall survival has yet been seen, but there is a trend in favor of bisphosphonate (HR 0.60, 95% CI 0.32–1.11; p = 0.11).

The results of the study have caused both patients and breast cancer support groups to demand the use of bisphosphonates as adjuvant therapy. The recommendations of the Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (German Gynecological Oncology Research Group) (AGO) already mention the possible adjuvant use of zoledronic acid 4 mg every 6 months [6]. However, use of the bisphosphonate for preventing metastases or as adjuvant treatment in breast cancer does not yet have approval. Until such time, insurance companies will sometimes decline applications to meet the costs. As a result, patients are forced to bear the costs themselves or hospitals and practice-based doctors have to face the risk of not being paid.

As well as the demonstration of clinical efficacy, one possibility for strengthening the basis of negotiation with the cost bearers would be the presentation of a positive cost-utility for bisphosphonate. The present study pursued this aim from the perspective of the German healthcare system, by calculating the cost-utility of zoledronic acid as adjuvant therapy for premenopausal women with breast cancer on the basis of clinical data from the ABCSG-12 study, and taking into account the German health utilities, the adverse effects, and the resources required.

Material and Methods

Model

In order to calculate the cost-utility of zoledronic acid as adjuvant therapy, we developed a Markov model [7].

Five different states of health were assumed (fig. 2). In the Markov model, a patient's state of health can change at any time or she can die of

breast cancer or any other cause. A timeline of 25 years was used to establish the long-term effects of the therapy.

The results were calculated as cost per QALY. The model is based on the following assumptions:

– All patients are premenopausal and have HR+ breast cancer.
– Aftercare is given according to the current S3 guideline [8].
– Measurements of the bone mineral density by dual-energy X-ray absorptiometry (DXA) scan are made at baseline, and after 6 and 12 months.
– Undesirable adverse effects occur only during the treatment.
– The discount rate is 3%, as recommended by IQWiG [4].
– All costs are based on data from the German healthcare system for the year 2009.

Model Inputs

Clinical data for the model are based on the results of the ABSCG-12 study [5]. The model was calculated for a duration of treatment of 3 years and a shown clinical benefit up to 7 years according to the maximal follow-up of the study.

The following clinical efficacy parameters were used:

– DFS: 54/899 events with zoledronic acid versus 83/904 events without zoledronic acid (HR 0.643, 95% CI 0.46–0.91)
– Recurrence-free survival: 54/899 events with zoledronic acid versus 82/904 events without zoledronic acid (HR 0.653, 95% CI 0.46–0.92)
– Overall survival: 16/899 events with zoledronic acid versus 26/904 events without zoledronic acid (HR 0.595, 95% CI 0.32–1.11)

The medication and administration costs were calculated according to the 4 arms of the study (fig. 1):

– All patients had goserelin 3.6 mg every 28 days (equivalent to 37 doses, including baseline),
– tamoxifen 20 mg/day + zoledronic acid 4 mg every 6 months (equivalent to 7 doses),
– tamoxifen 20 mg/day,
– anastrozole 1 mg/day + zoledronic acid 4 mg every 6 months (equivalent to 7 doses).

Medication costs at pharmacy selling price including VAT were taken from the standard source German Medicines Compendium (Rote Liste) [9] as of 2009.

Costs for administration, diagnostic investigation and treatment were calculated based on the German physicians fee scale (EBM) of 2009 for outpatient services.

Inpatient services were calculated on the basis of the German diagnosis-related groups (DRG) system.

Only those costs that are reimbursed by the insurance companies were integrated in the model. Patients' own out-of-pocket spending was not included.

All adverse effects associated with zoledronic acid and reported with an incidence of more than 5% in the ABCSG-12 study were taken into

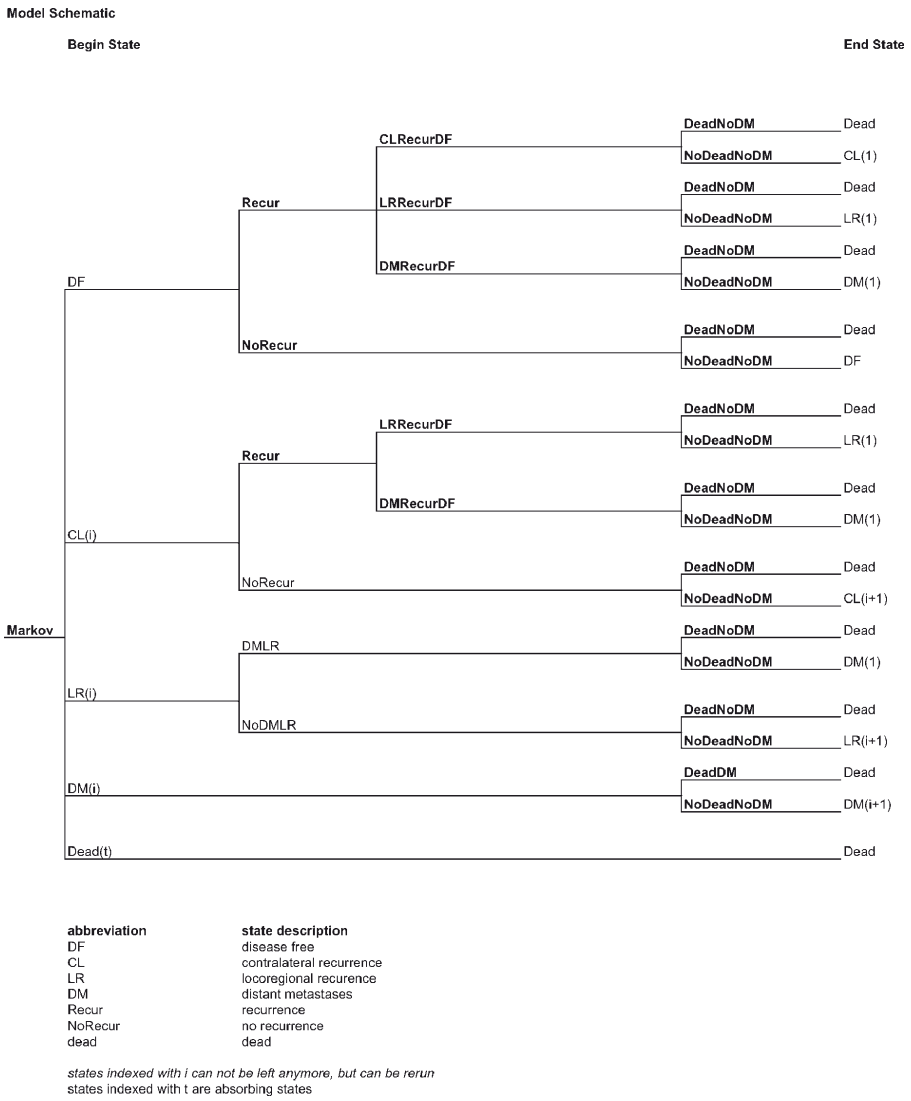


Fig. 2. Tree diagram of the Markov model.

account. The expert panel furnished the adverse effects with conventional diagnostic investigation and treatment, and the corresponding costs were calculated.

Due to the lack of availability of health utilities for women treated in Germany, and the assumption that these differ from other countries, the health utilities were determined in a pilot study at the University Breast Center of Franconia, using a visual analog scale (VAS). The state of health of 95 patients – with an initial diagnosis of breast cancer, in aftercare, with recurrent disease or contralateral breast cancer, with metastases, and in end-of-life (palliative) care – was determined by means of a questionnaire or interview. The utilities were then linked to the state of health in the model in order to calculate the corresponding QALYs. In cases where adverse effects occurred, a reduction of –0.01 in the state of health was calculated [10].

Sensitivity Analyses

Sensitivity analyses were conducted in order to test the uncertainty of the model inputs. A simple standard deviation was used for most cost parameters. For clinical efficacy parameters, a beta distribution was used. Costs for drugs and administration that were required in the underlying ABCSG-12 trial were not varied. The probability calculations were made using a Monte Carlo simulation with 1000 scenarios. The results present the different estimated costs and utilities.

The validity of the model is demonstrated with a cost-effectiveness acceptability curve. This shows the probability that the incremental cost-effectiveness ratio (ICER) will not exceed a defined threshold (€ 5000).

Results

Model Parameters

The costs calculated for clinical care are presented in table 1. These include the costs of medication as well as the costs of diagnostic investigations (laboratory tests such as for creatinine), and other patient care (medical history, physical examinations, administration of drugs, prescriptions, etc.).

The costs identified for aftercare measures as well as for the occurrence of disease-specific events (recurrence, contralateral breast cancer, metastasis, and end-of-life care, i.e. best supportive care) are also presented in table 1.

The health utilities as determined on a VAS at the University Breast Center in Franconia are given in table 2.

Cost-Utility Analysis

Total costs for zoledronic acid as adjuvant therapy for premenopausal women with HR+ breast cancer were determined at € 2262, for a period of 3 years, in line with the ABCSG-12 study.

Taking into account the clinical efficacy, the adverse effects, quality of life, and a timeline of 25 years, the use of

Table 1. Costs of the model: medicines, drug administration and event

Description of costs	Input variable, €
Cost of zoledronic acid medication per prescription[a]	350.14
Cost of zoledronic acid administration per prescription[a]	41.88
Cost of tamoxifen medication per prescription[b]	21.46
Cost of tamoxifen adminstration per prescription[b]	50.76
Cost of anastrozol medication per prescription[b]	606.77
Cost of anastrozol adminstration per prescription[b]	34.83
Cost of goserelin medication per prescription[b]	560.93
Cost of goserelin adminstration per prescription[b]	83.66
Annual cost per year in disease-free state	360.92
Annual cost for first year in contralateral recurrence state	20,408.41
Annual cost per year in contralateral recurrence state, year 2+	2514.65
Annual cost for first year in locoregional recurrence state	17,090.80
Annual cost per year in locoregional recurrence state, year 2+	2514.65
Annual cost for first year in distant metastases state	19,514.27
Annual cost per year in distant metastases state, year 2+	19,514.27
Cost of dying from breast cancer	10,397.75
Annual cost of arthralgia year 1	58.12
Annual cost of bone pain year 1	58.12
Annual cost of bone pain year 1	46.62

[a]Prescribed and applied every 6 months (182.5 days).
[b]Prescribed and applied every 3 months (90 days).

Table 2. Health utilities of the model[a]

Situation	n	Utility (median)	Minimum	Maximum	Reduction (compared with no event)
No event = unremarkable, in follow-up	42	0.720	0.120	1.000	–
Initial diagnosis of breast cancer	14	0.560	0.245	0.900	–
Contralateral cancer	4	0.550	0.410	0.695	–23.6%
Recurrence	17	0.540	0.100	0.840	–25.0%
Distant metastases	15	0.570	0.130	0.745	–20.8%
End-of-life (palliative) care	3	0.150	0.130	0.260	–79.2/
Death	–	0	–	–	–

[a]Investigated in an independent study at the University Breast Center in Franconia (Lux et al., unpublished data).

zoledronic acid achieves an ICER of –€ 45.83/QALY (95% CI –€ 1838 to € 2375; 0.02–0.41 QALY). It is therefore the dominant treatment strategy, compared with no bisphosphonate adjuvant therapy at all.

Sensitivity Analysis

The results of the sensitivity analysis using a Monte Carlo simulation and 1000 scenarios are presented in figure 3. The distribution shows a homogeneous picture of the cost-utility, which confirms the validity of the model. The parameters and their distribution are presented in table 3. Moreover, the

Table 3. Parameters and their distribution in sensitivity analysis

Variable description	Distribution	Standard error	a	b	n
Intercept parameter from AFT Weibull regression on DFS for NoZOL from ABCSG-12	normal	0.1707			
Scale parameter for AFT Weibull regression on DFS for NoZOL from ABCSG-12	normal	0.0684			
Relative risk of recurrence for ZOL vs. NoZOL from ABCSG-12	LnormSEonLogScale	0.1764			
Percent of recurrences from that are CL for ZOL	beta		108,8800	791,1200	899,0000
Percent of recurrences from that are LR for ZOL	beta		256,3977	643,6023	899,0000
Percent of recurrences from that are DM for ZOL	beta		612,3208	287,6800	899,0000
Percent of recurrences from that are DM for ZOL	beta		221,1833	678,8367	899,0000
Percent of recurrences from that are CL for NoZOL	beta		100,4400	804,5600	904,0000
Percent of recurrences from that are LR for NoZOL	beta		193,9888	711,0112	904,0000
Percent of recurrences from that are DM for NoZOL	beta		603,6667	301,3333	904,0000
Percent of recurrences from that are DM for NoZOL	beta		315,4348	599,5652	904,0000
Annual probability of recurrence from CL state, years 1–5	beta		115,2724	3034,7276	3,148,0000
Annual probability of recurrence from CL state, years 6–15	beta		71,3704	2564,6295	2,616,0000
Annual probability of recurrence from LR state, years 1–5	beta		130,6564	920,3438	1,049,0000
Annual probability of recurrence from LR state, years 6–15	beta		36,0432	431,9588	466,0000
Annual probability of death from DM state	beta		53,5000	198,5000	250,0000
Probability of arthralgia with ZOL	beta		315,6500	585,3500	899
Probability of arthralgia with no ZOL	beta		227,0000	679,0000	904
Probability of bone pain with ZOL	beta		216,7600	684,2400	899
Probability of bone pain with no ZOL	beta		163,7200	742,2800	904
Probability of fever with ZOL	beta		81,9100	819,0900	899
Probability of fever with no ZOL	beta		19,0800	886,9200	904
Annual cost per year in DF state	normal	92,0731			
Annual cost for first year in CL	normal	5,206,3227			
Annual cost for first year in LR	normal	4,359,9781			
Annual cost for first year in DM	normal	4,978,2216			
Annual cost per year in DM state, year 2+	normal	4,978,2216			
Cost of dying from breast cancer (DM) – assigned at transitions from DM to dead	normal	2,652,5360			
Annual cost of arthralgia year 1	normal	14,8268			
Annual cost of bone pain year 1	normal	14.83			
Annual cost of fever year 1	normal	11.89			
Decrement in utility with DF vs. perfect health	normal	0.0714			
Decrement in utility first year in CL vs. DF – applied first year in state	normal	0.0434			
Decrement in utility first year in LR vs. DF – applied first year in state	normal	0.0459			
Decrement in utility first year in DM vs. DF – applied first year in state	normal	0.0383			
Decrement in utility subsequent years in DM vs. DF – applied each subsequent year in state	normal	0.0383			
Decrement in utility with arthralgia year 1	normal	0.0026			
Decrement in utility with bone pain year 1	normal	0.0026			
Decrement in utility with fever year 1	normal	0.0026			

NoZOL: No zoledronic acid; ZOL: zledronic acid; CL: contralateral recurrence; LR: locoregional recurrence; DM: distant metastases; DF: disease free; LnormSEonLogScale: lognormal distribution with standard error input on log scale.

influence of the discount rates on the ICER was tested and the results are shown in table 4.

The resulting cost-effectiveness acceptability curve shows a probability of 62% that the ICER will not exceed the threshold of € 5,000 (€ 22,000 with a probability of 90%) (fig. 4). The CI of the ICER is –€ 91,900 to € 5,792.68 per QALY gained.

Discussion

Bisphosphonates are substances well established in the treatment of bone metastases and of osteoporosis. Preclinical data in recent years increasingly show that bisphosponates have a broader spectrum of activity than just their antiresorptive properties in the bone system. Bisphosphonates seem to have a direct toxic effect on tumor cells. In vitro, an antineoplastic effect has already been demonstrated in cell lines from carcinomas of the breast, prostate and pancreas, myelomas and osteosarcomas [11–14]. Several theories have been developed to explain the effect of bisphosphonates on tumor growth. Antineoplastic effects through both the induction of apoptosis and the inhibition of the invasive potential of tumor cells have been found in vitro [14]. Observations from the in vitro studies have been confirmed by in vivo studies [15].

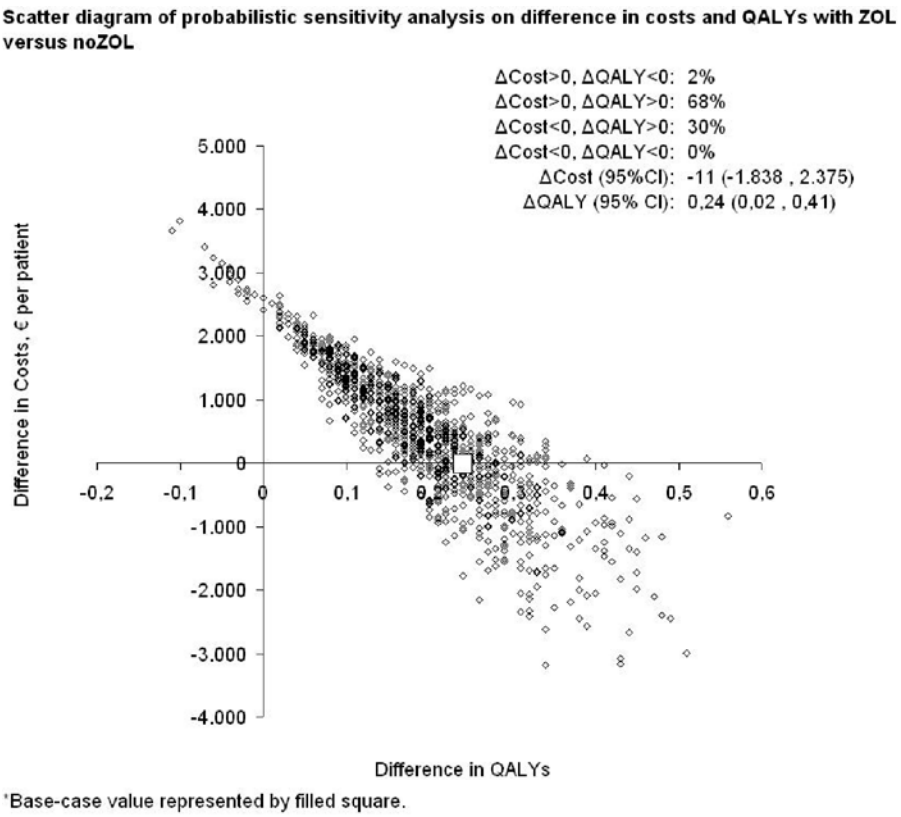
In the following, the effects of biphosphonates as adjuvant therapy in patients with breast cancer have been investigated using clodronic acid. The first results in 1998 already showed a reduction in bone metastases (7% versus 17%, $p < 0.002$) and visceral metastases (13% versus 29%, $p < 0.001$) [16]. Checking these results in a larger multicenter study was the logical next step. The ABCSG-12 study compared the clinical efficacy of an aromatase inhibitor with tamoxifen, with and without bisphosphonate therapy for both drugs, in premenopausal women with HR+ breast cancer. The impressive results mentioned previously were seen after a follow-up of 48 months. Understandably, publication of the results was followed by calls for the wide use of bisphosphonates as adjuvant therapy. However, when regulatory approval is lacking, clinical data are often not enough for the health insurers to agree to cover the costs. Self-payment will financially overburden many patients, depending on their social background. Analysis of cost-effectiveness as well as demonstration of a positive cost-utility can provide the additional data needed to support claims for coverage.

The result of the model presented here, –€ 45.83 per QALY (dominant strategy), shows a saving in costs with a simultaneous increase in the quality of life, thus confirming the

Table 4. Impact of different discount rates on the ICER

Discount rate, %[a]	Δ Costs, €	Δ QALY	ICER, €/QALY
1	–130	0.32	–406.25
3	–11	0.24	–45.83
5	123	0.19	647.37
10	448	0.10	4,480.00

[a]Discount rate applied for both costs and effectiveness.



*Base-case value represented by filled square.

Fig. 3. Sensitivity analysis of the cost-utility model.

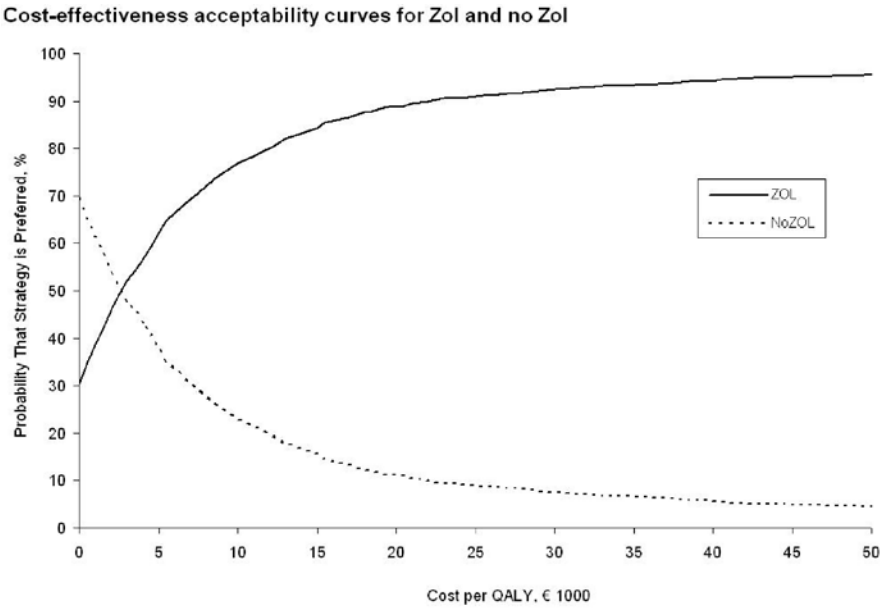


Fig. 4. Cost-effectiveness acceptability curve of zoledronic acid as adjuvant therapy.

Curves represent proportion of simulations (n=1000) for which each strategy is preferred given the willingness to pay (WTP) for a QALY shown on horizontal axis.

pharmacoeconomic relevance of bisphosphonates from the viewpoint of the German healthcare system. This can also be seen in the cost-effectiveness acceptability curve (fig. 4), which shows that the cost per QALY gained does not exceed the threshold value of € 5000 with a probability of 62% and € 22,000 with a probability of 90%. These results should be taken into account in routine clinical practice when deciding whether or not to use zoledronic acid as adjuvant therapy and they can also strengthen the case when asking the health insurers to meet the costs.

From the perspective of health economics, innovative treatment shown to be the dominant strategy is extremely efficient, as savings can be achieved in this way. By way of comparison, aromatase inhibitors, which have an established place in all recommendations and treatment guidelines for postmenopausal women with HR+ breast cancer, have a cost-utility of € 7000–20 000 per QALY [17], depending on the country and model used, and this is considered to be cost effective.

Furthermore, it is must be remembered that the model presented here used the endpoints of the ABSCG-12 study as the clinical efficiency parameters (DFS, recurrence-free survival and overall survival). Other potential positive bisphosphonate effects such as those on bone metabolism were not taken into account. Oncological treatment of premenopausal women (chemotherapy, gonadotropin-releasing hormone (GnRH) analogs) leads to a significant long-term risk of osteoporosis due to hypogonadism [18]. GnRH analogs are associated with a clear reduction in spinal bone mineral density, which can already be seen within 6 months. In a clinical trial of GnRH analogs, after a follow-up of 2 years, Fogelman and co-workers found that the bone mineral density on treatment with goserelin was reduced by 10.5% in the lumbar spine and by 6.4% in the neck of the femur [19]. In addition, many premenopausal women are given chemotherapy that can lead to persistent amenorrhea, depending on the age of the patient, the product used, and the duration of treatment. These patients show a 10% lower bone mineral density in the lumbar spine than healthy women of the same age [20]. The reduction of the maximum attainable peak bone mass, especially in young women, can lead to a higher risk of osteoporosis in later life, with the associated risk of fracture. Major costs for the healthcare system can result from the treatment and rehabilitation required, as well as from the danger of a person becoming immobile and needing long-term nursing care. Osteoporosis and its sequelae cost the German healthcare system € 1.4 billion each year [21]. Prophylaxis with bisphosphonates is advised if the fracture risk is 30% or more. A recommendation that bisphosphonates be considered for preventing iatrogenic bone loss can be found in the current AGO recommendations [6]. This shows high cost-effectiveness (€ 3849 per QALY), especially in young women [22]. Due to the lack of data in premenopausal women, prevention of osteoporosis was not taken into account in our model. It is possible, however, that the cost-utility of zoledronic acid is actually higher than we found, thanks to its potential positive effects on bone health.

The sensitivity analyses on the model show a high validity. However, comparisons with other cost-utility models on the use of a bisphosphonate as adjuvant therapy in patients with HR+ breast cancer are desirable. There are only a few published data because of the contemporary nature of the problem and the findings. The ABSCG-12 study is the only multicenter prospective randomized trial available for pre-

menopausal women. A similar model for the USA, also based on the results of the ABSCG-12 study, was presented by Delea and co-workers at the San Antonio Breast Cancer Symposium in 2008 [23]. Their model was based on the inclusion of 3 years' therapy with zoledronic acid every 6 months in comparison with endocrine therapy alone. The cost-utility was calculated from the standpoint of the American healthcare system using a Markov model. In their first scenario, calculations were made on the assumption that the benefits of bisphosphonate last only for the maximum duration of follow-up in the ABSCG-12 study. With total costs of $ 5193 for medication and drug administration, and a cost-utility of $ 7794 per QALY, their results are comparable to those of our model. The higher costs per QALY are because the American healthcare system is more expensive, including higher costs for zoledronic acid and its administration ($ 907.99 versus €392.02 per dose), aftercare ($ 2898.00 versus € 369.92 per year) and treatment of distant metastases ($ 80,493.00 versus €39,028.54). Delea et al. also calculated the cost-utility in a second scenario, assuming that benefits would last for life. This leads to a gain of 1.53 years of life, combined with a reduction in costs for the healthcare system of $ 2127 per patient.

One limitation of the model is that the efficacy data is based on only one trial (ABSCG-12). Although there are several published studies available for postmenopausal women, this is the only multicenter, randomized phase III trial that has analyzed the use of bisphopshonates in the adjuvant setting of premenopausal women. Further data is necessary to confirm these results. Regarding the use of bisphosphonates in postmenopausal women, data on its clinical efficacy already exist. In the ZO-FAST study, 1065 postmenopausal women on treatment with the aromatase inhibitor letrozole were given zoledronic acid in order to investigate the prevention of osteoporosis [24]. Patients were randomly allocated to zoledronic acid (4 mg every 6 months for 5 years) either upfront or delayed until after their T-score dropped to below –2.0. After 36 months, a significant improvement in the bone density was seen with early bisphosphonate therapy (lumbar spine $p < 0.0001$ and hip $p < 0.001$). Secondary clinical endpoints such as recurrence-free survival and DFS were also looked at. There was a significant reduction of recurrence (22 (4.2%) versus 37 (7.5%) events; $p = 0.0423$) and improvement in DFS (26 (4.9%) versus 43 (8.1%) events; $p = 0.0336$) in patients who started therapy with zoledronic acid immediately. During the San Antonio Breast Cancer Symposium in 2008, data were presented on the combination of zoledronic acid with chemotherapy as neoadjuvant therapy. In the AZURE study, a multicenter randomized clinical trial, 3360 pre- and postmenopausal women were given zoledronic acid in addition to their standard therapy, as neoadjuvant or adjuvant therapy, over a period of 5 years [25]. 205 patients received bisphosphonate as neoadjuvant therapy. Patients were given zoledronic acid every 3–4 weeks in addition to the chemotherapy. The addition of bisphosphonate achieved a significant 33% reduction in tumor size (14.1 mm, $p = 0.002$). The rate of complete remission was also significantly increased (10.9% versus 5.8%, $p = 0.033$).

These data have led to the AGO recommendation that bisphosphonate therapy can also be considered as a therapeutic option for postmenopausal women, and this is even recommended by an interdisciplinary consensus [6, 16]. As the effects of biphosphonates on breast cancer-specific events were not the primary objective in either study, as yet there are no results from studies with the primary objective of demonstrating such effects in the postmenopausal population, and which could be used as a basis for a cost-utility model. A high cost-utility is to be expected, not only because of the clinical efficacy but also because of the protection against the progressive loss of bone density seen on treatment with aromatase inhibitors. This may even be in the negative range, i.e. an improvement in QALY combined with cost savings.

Conclusions for Clinical Practice

The use of biphosphonates as adjuvant therapy for patients with breast cancer has considerably increased, not least because of the results of the ABSG-12 study. However, the indication does not yet have regulatory approval. In conflict with this are the understandable demands from patients and breast cancer support groups who want bisphosphonates used as adjuvant therapy. In this situation, possible options are self-financing by the patient, administration of the drug without a confirmation of cost coverage (and the associated risk of doctors not being paid), or filing a claim for costs with the health insurance, which leaves the question of financing open once again if the application is rejected. Our model shows that using zoledronic acid as adjuvant treatment can save resources for the German healthcare system, because of its good clinical efficacy and its relatively low costs due to the 6-monthly dose intervals. Providing data on costs in addition to the clinical findings, our data should help to support claims for health insurers to meet the costs and may even force regulatory approval in the near future.

Conflict of Interest

This model was designed with financial support from Novartis Oncology (statistical analysis, expenses for travel and effort). The expert panel of the model are independent clinical physicians.

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