original article

Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial

K. J. Dedes[1]*, T. D. Szucs[2], P. Imesch[1], A. Fedier[1], M. K. Fehr[1] & D. Fink[1]

[1]*Division of Gynecology, Department of Obstetrics and Gynecology, University Hospital of Zurich, Zurich;* [2]*Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland*

Background: Routine adjuvant administration of trastuzumab (T) has been implemented in most centers, but its economic impact has not yet been well examined.

Methods: A Markov model was constructed based on clinical data of the Herceptin Adjuvant (HERA) and the Finland Herceptin (FinHer) trials. Costs from the perspective of a Swiss health care provider were calculated based on resource use.

Results: On the basis of HERA data, our model yielded an overall survival rate of 71.8% for the T group versus 62.8% for the control group [risk ratio (RR) = 0.87] after 10 years and 62.9% versus 52.7% (RR = 0.84) after 15 years. Cost-effectiveness resulted in 40505 Euros (EUR) per life years gained (LYG) after 10 years and 19673 EUR per LYG after 15 years. For the FinHer regimen, overall survival after 10 and 15 years resulted in 81.8% versus 66.1% (RR = 0.81) and 73.6% versus 57.0% (RR = 0.77). Costs of 8497 EUR per patient could be saved after 10 years and 9256 EUR after 15 years compared with the control group.

Conclusion: In a long-term perspective, adjuvant T based on the HERA regimen can be considered cost-effective. The regimen used in the FinHer trial is even cost saving, but estimations are based on a single small trial.

Key words: adjuvant treatment, breast cancer, cost-effectiveness, trastuzumab

introduction

Trastuzumab (T) (Herceptin®, Roche, Switzerland), a humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2), is an important cell proliferation regulator in HER2-overexpressing breast cancer [1]. HER2 overexpression occurs is ~25% of breast cancers and is associated with a poorer prognosis compared with HER2-nonexpressing tumors [2]. So far, T is routinely used for patients with HER2-positive metastatic breast cancer, showing good efficacy and tolerability given as monotherapy as well as in combination with chemotherapy [3]. The major side-effect is cardiotoxicity occurring in up to 20% of patients [4].

Recently, interim results from randomized, multicenter trials examining T as an adjuvant treatment in early stage breast cancer overexpressing HER2 have been published [5–7]. Thereafter, T has been implemented as a standard adjuvant treatment in combination with chemotherapy for early-stage breast cancer in many countries.

As for other monoclonal antibodies, wholesale drug costs per cycle for T are high compared with other chemotherapeutic

agents [8]. Neyt *et al.* [9] analyzed the incremental costs for health care providers, resulting from the introduction of T in adjuvant therapy in Belgium. They found an incremental cost of 45 000 Euros (EUR) per patient compared with standard regimens as doxorubicin plus cyclophosphamide or carboplatin plus docetaxel.

However, a cost-effectiveness analysis taking into account the long-term clinical benefits and the side-effect profile of T based on both the Herceptin Adjuvant (HERA) trial and the Finland Herceptin trial (FinHer) has not been published while this topic is being discussed at conferences [10–12].

materials and methods

We developed a Markov decision model to estimate the cost-effectiveness of adjuvant treatment of T for women with HER2-positive early breast cancer [13, 14]. Two strategies were examined: adjuvant treatment after surgical therapy of early breast cancer with or without T. Clinical data and the treatment protocol were based on the interim results of the HERA, FinHer trial and the published literature (Table 1). We simulated a hypothetical cohort of 10 000 women of an average age of 50 year with the same entry criteria as in the HERA and FinHer trial for a period of 15 years (Markov cycles). The cycle length was 1 year and the applied possible disease stages were disease-free survival, local recurrence, regional recurrence, metastatic disease and death. For each year, we calculated the transition probabilities of the different disease states according to Table 1. Contralateral breast cancer

Correspondence to: Dr K. J. Dedes, Division of Gynecology, Department of Obstetrics and Gynecology, University Hospital of Zurich, Frauenklinikstrasse 10, CH-8091 Zurich, Switzerland. Tel: +41-44-255-52-00; Fax: +41-44-255-44-33; E-mail: konstantin.dedes@usz.ch

Table 1. Survival estimates, recurrence and mortality rates used in the Markov model

Reference	Outcome	Annual probabilities			
		HERA data		FinHer data	
		Trastuzumab group	Observational group	Trastuzumab group	Observational group
	After adjuvant treatment				
[5, 7]	Local recurrence	0.01	0.022	0.003	0.009
	Regional recurrence	0.006	0.008	0.003	0.009
	Metastatic disease	0.05	0.091	0.023	0.075
	Death rate for first year	0.017	0.022	0.017	0.040
[15]	Yearly mortality for 2nd–15th year rate (Swiss 50-year-old women)	0.0018 (50 years) to 0.0067 (65 years)			
	After treatment of local recurrence				
[16]	Disease free	0.9			
	Regional recurrence	0.06			
	Metastatic disease	0.01			
	Death	0.03			
	Outcome after treatment of regional recurrence				
[17]	Disease free	0.9			
	Local recurrence	0			
	Metastatic disease	0.05			
	Death	0.05			
	Outcome after treatment of metastatic disease				
		Trastuzumab for metastatic disease		No trastuzumab for metastatic disease	
[3]	Metastatic disease	0.78		0.67	
	Death	0.22		0.33	

HERA, Herceptin Adjuvant; FinHer, Finland Herceptin.

was not considered. As in the FinHer study, events were published after a mean follow-up of 3 years; 1 year probabilities were calculated. Furthermore, as recurrences in the FinHer study were not separately reported as local or regional recurrences, we assumed that half of the recurrences were regional. Costs occurring in each cycle considering different disease states were calculated. The clinical outcome of our simulated model (e.g. overall survival and local recurrence) was validated with published case series.

clinical data

Disease-free survival, recurrent disease and mortality in both strategies were based on published 1-year data of the HERA trial and 3-year data of the FinHer-trial [5, 7]. Based on survival and recurrence patterns of a large meta-analysis for early breast cancer patients, we assumed a constant yearly risk for local and distant recurrences for the first 5 years after adjuvant treatment [18]. Thereafter, this risk was gradually reduced by 10% from 6th to 15th year in order to reflect the flattening of recurrence curve in breast cancer patients after 5 years [18]. Female mortality rates for 50- to 65-year-old Swiss women were derived from the life tables published by the Swiss Federal Statistic Office [15]. The clinical benefit of T was assumed to last for the first 5 years in the base case, thereafter the relative risk for recurrent and metastatic disease in the T group assumed to be the same as in the observational group. This duration of benefit for T was indicated by the National Institute for Health and Clinical Excellence (NICE) [19]. As preliminary data of the HERA trial indicates that the hazard ratio for disease-free survival of the T group is similar to that of the observational group after 2–3 years, we conducted a scenario analysis with a 3-year benefit only [20]. Survival probabilities for patients with local and distant recurrent disease were extracted from the available literature (Table 1). Congestive

heart failure (CHF) was the only side-effect of T taken into account, occurring in 1.7% of patients receiving T during the 1st year of treatment [5]. We assumed that in these cases medical treatment for CHF was carried out for 1 year, as T's cardiotoxicity is usually reversible [21]. To date, in all available studies with adjuvant T treatment, no death due to CHF occurred; hence, mortality due to side-effects was assumed to be zero. The percentage of estrogen-positive breast cancer patients was ~50% [5, 7].

cost parameters

Direct medical costs were calculated from the perspective of a Swiss health care provider in EUR (CHF/EUR exchange rate 2006 : 1.55) as follows: Prices of T (5.1 EUR/mg) and other drugs were derived from official Swiss pharmacy prices [22]. Cost of hospitalization, surgery for recurrent and metastatic disease, radiotherapy, diagnostics and palliative chemotherapy were estimated based on resource utilization and multiplied by the official Swiss reimbursement catalogue [23]. Charges were used as a proxy for costs, as true opportunity costs are not readily available. We did not determine indirect costs, such as those due to time off from work, travel and other out-of-pocket expenses.

trastuzumab group. Cost of ambulatory administration of adjuvant T according to the regimen used in the HERA trial (8 mg/kg loading dose and 6 mg/kg every 3 weeks) and the FinHer trial (4 mg/kg loading dose and 2 mg/kg weekly for eight cycles) including doctor's visit and blood examination at every cycle and electrocardiography before the first cycle were calculated. Cost of echocardiography (245 EUR) every 3 months and FISH analysis (150 EUR) was considered as well. For the HERA regimen, a 440 mg and 150 mg vial of T (590 mg/8 mg/kg = 73.7 kg) was calculated for the loading dose, whereas for the 6-mg/kg dose only a 440 mg

(440 mg/6 mg/kg = 73.3 kg) vial was applied. To consider additional vial use for women weighing >74 kg, we assumed the use of an additional 150 mg vial in 15% of patients, as previously described [24]. For the FinHer regimen, a 440 mg vial was calculated for the loading dose and a 150 mg vial for each following administrations. As our hospital pharmacy delivers sterile bottled vials per order in milligrams, the cost of redundant drug due to uniform vials (150 mg and 440 mg) of the manufacturer can be saved. This fact was assessed in the scenario analysis. Treatment withdrawal was reported to be 8.5% in the HERA trial, which we incorporated as discontinuations after mean 6 months in these patients.

Cost for the treatment of symptomatic CHF was extracted from the literature. Based on a randomized trial comparing medical treatment with high-dose versus low-dose angiotensin-converting enzyme (ACE) inhibitor, a cost analysis was conducted for Switzerland. The costs of treating patients with symptomatic CHF including high-dose ACE inhibitor and hospitalization amounted to 4320 EUR yearly and was included in our cost calculation by adjusting to 2006 by 3% yearly price inflation [25]. Furthermore, cost of echocardiography every 3 months for the T group was considered as well. Cost for breast surgery, adjuvant chemotherapy and radiotherapy were not included, as these costs accrued in both the T group and the control group.

disease-free survival and local or regional recurrence. For patients with disease-free survival, we calculated yearly costs of a 5-year hormonal therapy with aromatase inhibitor for hormone receptor-positive patients (2195 EUR per year), yearly gynecological examination and mammography [26]. For patients with local and regional disease, we estimated costs for diagnosis including mammography and sonography, surgery including hospitalization, radiotherapy and 5-year hormonal therapy with aromatase inhibitors.

metastatic disease. As patients with metastatic disease present with various patterns of metastasis, therapy depends on the site of metastasis. In order to obtain 'real world' data, we collected resource use of patients presenting with metastatic disease from the year 2000 to 2004 after adjuvant treatment of stage I–III breast cancer in our clinic (n = 21) through comprehensive retrospective patient's chart review. We included total resource use occurring during the first 5 years of treatment for metastatic disease and calculated yearly costs. Yearly costs for treatment of patients with metastatic disease resulted in 13 025 EUR per patient excluding T use. This yearly cost was applied to cases with metastatic disease not receiving T for metastatic disease. We did not exclude HER2-negative cases because of a low number of patients, but costs of treatment in the metastatic setting does not significantly differ between HER2 positive and negative apart from T administration. In order to adapt the costs for metastatic disease of HER2-positive breast cancer patients to current standards, we added virtually the costs of T for metastatic disease for the first year of treatment. As T has no proven effect on brain metastasis and not all metastatic patients receive T due to terminal disease, we assumed that 80% of HER2-positive metastatic patients receive first-line T administrated for 40 weeks (6 mg/kg every 3 week after a 8 mg/kg loading dose) in average [3, 27]. First-year treatment costs for metastatic disease, including T treatment therefore amounted at 41 412 EUR per year and thereafter 13 025 EUR yearly. As it is yet unclear whether patients receiving T as adjuvant therapy will be retreated with T for metastatic disease and whether efficacy will be similar to T-naive patients, we decided to use in the base case a retreatment rate of 50%. The NICE indicated a retreatment rate of both 100% and 0% as unrealistic [19]. In the scenario analysis, a retreatment rate of 80% and 20% is also examined (Table 5).

discounting

Discounting for the time, value of money was applied to costs in order to compare alternative future levels of costs. In this analysis, an annual discount rate of 3.0% was applied to all costs. Discounting of effectiveness was included in the sensitivity and the scenario analysis.

Table 2. Cost parameters used for different health states

Disease free survival (gynecological examination, mammography and aromatase inhibitor)	1345 EUR per year
Local recurrence (imaging, surgery, hospitalization, radiotherapy, aromatase inhibitor)	7280 EUR for first year
Regional recurrence (imaging, surgery, hospitalization, radiotherapy, aromatase inhibitor)	13 640 EUR for first year
Metastatic disease (imaging, palliative surgery, radiotherapy, chemotherapy, hormonal therapy, hospitalization)	41 412[a] EUR for first year in the control group, 27 219[b] EUR for first year in the T group and 13 025 EUR for further years in both groups

[a]T treatment rate of 80%.
[b]T retreatment rate of 50%.
EUR, Euros; T, trastuzumab.

Table 3. Clinical characteristics of included metastatic patients

Number of patients	21
Primary localization of metastasis	8 pulmonal metastasis
	8 bone metastasis
	3 liver metastasis
	1 brain metastasis
	1 peritoneal metastasis
Outcome	17 dead after mean survival of 11 months
	4 alive at follow-up of mean 48 months
Treatment (first and second line)	11/21 taxan-containing chemotherapy
	3/21 only symptomatic therapy
	9/21 bisphosphonate treatment
Mean total hospitalization time	30 days

sensitivity and scenario analysis

For the HERA regimen, we conducted univariate sensitivity analyses (±10%, ±20%, ±30%) for the following variables: prescription price of T, yearly cost of metastatic disease, the clinical efficacy of T and the cost of treatment of local/regional recurrence for the base case scenario. Effectiveness was discounted at 0% (as in base case), 3%, 5% and 7%. The base case included assumptions that had to be made due to poor evidence regarding future clinical data, treatment, etc. Therefore, we conducted several scenario analyses to consider these uncertainties.

For sensitivity analysis of the FinHer regimen, we applied the 5% and 95% confidence interval of the risk for recurrence and metastases into our model, instead of the ±30% as for the HERA data. This was done in order to better reflect the associated high uncertainties of our base case due to limited sample size of the FinHer trial.

results

base case for the HERA regimen

In our model, recurrence rates at 10 years are 10.44% for the T group versus 15.0% for the observational (C) group [risk ratio

(RR) = 0.70] and 11.3% versus 15.8% (RR = 0.71) at 15 years. Overall survival rate is 71.8% for T versus 62.8% for C (RR = 0.87) at 10 years and 62.9% versus 52.7% (RR = 0.84) at 15 years, respectively. Cost-effectiveness results are listed in Table 4. Costs for local, regional and metastatic disease are 51% lower in the T group compared with the C group. Costs in the T group are mainly generated by adjuvant T drug cost accounting for 39% of total costs. In the C group, treatment costs of metastatic disease account for 75% of total costs.

scenarios

Cost-effectiveness of different scenarios applied to our model is summarized in Table 5.

sensitivity analysis of the HERA regimen

In the sensitivity analysis, the cost-effectiveness of T is mainly influenced by its clinical efficacy, discounting of effectiveness and its prescription price (Figure 2). The model shows robustness for treatment cost of metastatic and local/regional disease.

Table 4. Cost-effectiveness of adjuvant trastuzumab per patient based on the HERA trial regimen

	Total cost of trastuzumab group (EUR)	Total cost of comparator group (EUR)	Incremental cost (EUR)	LYG	Cost/ LYG (EUR)
Base case					
At 5 years	53 403	27 304	26 099	0.12	212 360
At 10 years	62 656	41 559	21 097	0.52	40 505
At 15 years	67 682	47 791	19 891	1.01	19 673

HERA, Herceptin Adjuvant; EUR, Euros; LYG, life years gained.

Table 5. Cost-effectiveness using different scenarios in cost per life year gained for the HERA regimen

| Scenarios examined	At 5 years (EUR)	At 10 years (EUR)	At 15 years (EUR)
Clinical benefit of T limited to 3 years	245 004	70 920	37 630
T retreatment (20%) for metastatic disease for patients with adjuvant T	233 746	39 124	17 521
T retreatment (80%) for metastatic disease for patients with adjuvant T	197 500	41 882	21 763
T administration in centers with sterile preparation of ordered drug dosage (saving redundant drug)	181 219	33 157	15 888
Discounting life years gained at 3%	245 396	51 443	27 094

HERA, Herceptin Adjuvant; EUR, Euros; T, trastuzumab.

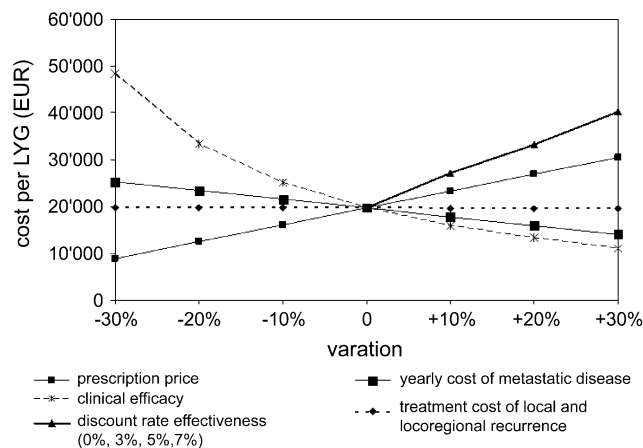## base case and sensitivity analysis for the FinHer regimen

For the FinHer regimen, recurrence rates at 10 years are 4.91 % for the T group versus 8.77% for the C group (RR = 0.55) and 5.48% versus 9.19% (RR = 0.60) at 15 years. Overall survival after 10 and 15 years were 81.8% versus 66.1% (0.81) and 73.6% versus 57.0% (0.77), respectively (Figure 1). Costs for T administration were 9248 EUR for this regimen compared with 39 245 EUR for the HERA regimen. Cost effectiveness results are listed in Table 6. Costs per patient for the T group were lower than those for the control group in the base case and sensitivity analysis, using the 5% and 95% confidence interval of the risk for local and distant recurrence [7].

model validation

HERA regimen. The local recurrences and overall survival rates obtained from our model for the control group are comparable to published large case series. Our 10-year local recurrence rate of 15.0% is somewhat higher than the 13% reported in a meta-analysis of HER2 positive and negative, node-positive early breast cancers [18]. However, the HERA patient population includes only HER2-positive patients, which is associated with
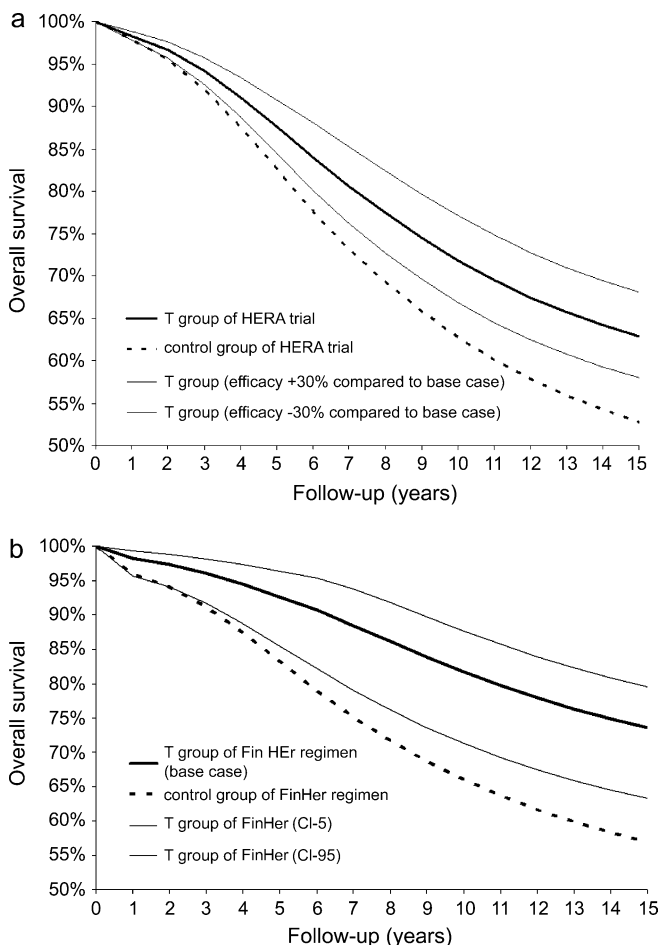
Figure 1. Overall survival projections based on the Herceptin Adjuvant (HERA) and the Finland Herceptin (FinHer) trials (fine lines indicate survival probabilities used in the sensitivity analysis). (A) HERA trial and (B) FinHer trial.

Figure 2. Univariate sensitivity analysis of the base case analysis of the Herceptin Adjuvant regimen.

Table 6. Cost-effectiveness of adjuvant trastuzumab per patient based on the FinHer trial regimen

	Total cost of trastuzumab group (EUR)	Total cost of comparator group (EUR)	Cost savings (EUR)	LYG
Base case				
At 5 years	20 070	23 816	−3746	0.27
At 10 years	28 210	36 707	−8497	0.97
At 15 years	33 419	42 675	−9256	1.79
5% CI of base case				
At 5 years	17 955	23 816	−5861	0.38
At 10 years	25 866	36 707	−10 841	1.36
At 15 years	31 348	42 675	−11 326	2.48
95% CI of base case				
At 5 years	23 653	23 816	−163	0.04
At 10 years	32 051	36 707	−4656	0.25
At 15 years	36 760	42 675	−5915	0.55

FinHer, Finland Herceptin; EUR, Euros; LYG, life years gained; CI, confidence interval.

higher recurrence rate, and therefore a recurrence rate of 15.0% should be regarded realistic for the HERA study control group. Overall survival in the control group of 62.8% after 10 years is similar to published data on HER2-positive early breast cancers ranging from 50% to 65% [28, 29].

FinHer regimen. Local recurrence rate of 8.8% in the control group is lower than the 13% reported in the literature [18]. Overall survival of 66% after 10 years in the control group is slightly higher than that of published data on HER2-positive early breast cancers ranging from 50% to 65% [28, 29].

discussion

Our findings in the base case analysis and the scenario analysis based on the HERA regimen indicate that the cost-effectiveness ratio after 5 years is above the generally accepted 50 000 EUR per life years gained (LYG) for new therapies [30, 31]. The main cost driver of adjuvant T treatment is the high prescription

price of this drug. However, this costly adjuvant treatment reduces risk of recurrences and metastasis, resulting in lower costs for secondary and palliative treatments. Therefore, the cost-effectiveness ratio improves in our calculation after 10 and 15 years to a threshold <50 000 EUR in both the base case and the sensitivity analysis. Our results indicate that adjuvant treatment may be more cost-effective on a 15-year horizon than in the metastatic setting only [24]. Endocrine treatment of estrogen receptor-positive early breast cancer for 5 years with anastrozole compared with the less costly tamoxifen resulted in 96 000 US$ per LYG after 12 years and 40 600 US$ after 20 years [32]. Compared with our results, this ratio is higher and still regarded as cost-effective for US health care system.

An important issue strongly influencing the cost-effectiveness is the dosage and number of cycles of T. Although patient number and unequally distributed nodal positive diseases were major limitations of the FinHer trial, the published data of this study considering 9 weeks of T administration are impressive [7]. Although not yet recommended as standard therapy, we attempted to estimate the cost-effectiveness of the FinHER regimen with the limited clinical data available. As recurrences are not reported in detail (local versus regional) and sample size is very limited, a cost-effectiveness analysis is associated with many uncertainties. Our model for the FinHer trial yielded a low 10- and 15-year recurrence rate compared with published literature. However, this rate is based on the six events of 116 (5.2%) patients after a mean follow-up of 3 years (H. Joensuu, personal communication; Helsinki). In the sensitivity analysis, we attempted to offset these high uncertainties by using the wide ranges of the reported confidence intervals.

Interestingly, our results indicate that this 9-week regimen might even save costs compared with no adjuvant T treatment. In contrast, the HERA regimen is more costly than no adjuvant T while being cost-effective. Thus, clinical and economic efficacy of the FinHer regimen should be confirmed by larger trials.

So far, Neyt et al. [9] conducted a cost analysis before the publication of the clinical data of the HERA trial for the Belgian health care system. They estimated combination chemotherapy with T to result in total cost of 45 000 EUR for 50 year old patients with stage III breast cancer. Depending on clinical efficacy, the authors concluded that T may be cost-effective. In our analysis, we used 39 000 EUR cost for T treatment additionally to standard chemotherapy, which is comparable to the calculation of Neyt et al. Hillner [10] estimated for the health care system of the United States, a cost-effectiveness ratio of 76 300 US$ per LYG after 10 years and 39 000 US$ per LYG after 20 years. The 10-year overall survival projections were similar to our model with 68% versus 57.2% in the T group versus C group. He also concluded that adjuvant T may be cost-effective in a long-term view. Furthermore, Norum and Olsen [11] found for the health care system of Norway a cost-effectiveness of 11 800–35 214 EUR per LYG; however, indirect cost was also considered in this cost analysis. A cost-effectiveness analysis for UK submitted by the manufacturer to the NICE and presented at a conference found 2396 £ (∼3600 EUR) per quality-adjusted LYG [12, 19]. However, these estimations assumed a lifetime benefit of T and a T retreatment rate for metastatic disease of 0%. The NICE committee

regarded these assumptions as too optimistic and recommended a 5-year benefit and indicated a retreatment rate of 100% more probable. Under these assumptions, T cost-effectiveness resulted in 18 942 £ (∼28 000 EUR) per quality adjusted LYG.

Our model yielded 17 000–38 000 EUR per LYG after 15 years for the HERA regimen under various assumptions, which is similar to the results reported by authors mentioned above, although that all these analyses were based on different health care systems. In contrast to these analyses, we did not use 20 year or even longer projections, as we assume a maximum benefit of T for the first 5 years instead of a lifelong benefit. LYG in the T group beyond our 15-year horizon is excluded in our analysis and the cost-effectiveness might be underestimated. However, we chose a conservative approach as the underlying patient population in a highly selected subgroup of breast cancer patients. Long-term data of HER2-positive versus -negative breast cancer patients are limited to 10 years, thus not allowing to validate survival projections longer than this time period. Furthermore, cost-effectiveness analysis of T for adjuvant treatment are modeling long-term impact of T treatment based on clinical data after 1–2 year follow-up. Uncertainties regarding these projections are increasing the longer the time horizon is chosen and accordingly the cost-effectiveness results.

In our base case scenario for the HERA regimen, we used a retreatment rate of 50% for patients receiving T for adjuvant therapy compared with the control group receiving in 80% of cases T for metastatic disease. However, poor evidence exists about retreatment rate and T resistance. As the NICE was cautious about 0% and 100% retreatment rate, the 50% is appropriate for the base case according to our opinion [19]. In the scenario analysis, cost-effectiveness results of 20% and 80% retreatment rates are also shown and may be more realistic than the 0% versus 100% submitted to the NICE by the manufacturer. However, retreatment rate of 80% may represent the most probable scenario in the near future, assuming that novel costly targeted therapies will be soon available for HER2-positive metastatic breast cancer resistant to T [33].

A crucial issue when considering cost-effectiveness of T is the projected duration of benefit. In our base case, we assumed a 5-year benefit as recommended by the NICE. However, recent data indicate the benefit to last not more than 2–3 years in the HERA trial [20]. In contrast, in the Joint analysis of the NSABP-B-31 and NCCTG-N9831 the benefit is still significant at 3 years and may last even longer [6]. Norum *et al.* used in their model, a benefit of T lasting 10 years and the manufacturer assumed a lifelong benefit in their base case. As shown in our scenario analysis with T's benefit lasting 3 years only, the cost-effectiveness is much less favorable, but still meets the acceptability threshold of 50 000 EUR per LYG.

Interestingly, the scenario analysis shows that a significant amount of money can be saved if T can be ordered by dosage (in milligram) through a pharmacy as in our institution. In contrast, the use of the two uniform vials (150 mg and 440 mg) provided by the manufacturer is often associated with loss of costly redundant drug.

However, our analysis has some limitations. It is based on clinical data of 1-year and 3-year analyses of two single randomized clinical trials. The long-term clinical benefit had to be estimated by modeling techniques. Nevertheless, adjuvant T has been approved in many countries based on this short-term clinical data and without any conducted cost-effectiveness studies.

Furthermore, costs were derived partially from standard treatment guidelines in the case of local and regional recurrence and partially from a retrospective chart review for metastatic disease. Our sample size of patients presenting with metastatic disease after adjuvant treatment of breast cancer is limited. However, we think that this sample might be a representative collection as these patients present with various patterns of metastasis (Table 3). Unfortunately, we had to rely solely on this data, as in Switzerland no disease-specific cost data exists.

We conclude that adjuvant T treatment may be cost-effective in a long-term perspective based on current clinical data from the HERA trial. The FinHer regimen clearly seems to save money compared with no adjuvant T treatment, although its clinical and economic efficacy should be supported by larger clinical trials.

acknowledgements

references

1. Leyland-Jones B. Trastuzumab: hopes and realities. Lancet Oncol 2002; 3: 137–144.

2. Slamon DJ, Godolphin W, Jones LA et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989; 244: 707–712.

3. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783–792.

4. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol 2004; 22: 322–329.

5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659–1672.

6. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673–1684.

7. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354: 809–820.

8. Cox MC, Figg WD, Thurman PW. No rational theory for drug pricing. J Clin Oncol 2004; 22: 962–963.

9. Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin in adjuvant setting: the Breast Cancer International Research Group 006 trial. Ann Oncol 2006; 17: 381–390.

10. Hillner BE. Clinical and cost-effectiveness implications of the adjuvant transtuzumab in HER2+ breast cancer trials. Breast Cancer Res Treat 2005; 94 (Suppl 1): S1–S287.

11. Norum J, Olsen JA. Trastuzumab in adjuvant breast cancer therapy: a model based cost-effectiveness analysis. J Clin Oncol 2006; 24: (Abstr 628).

12. Wardley AM, Cameron DA, Bell R et al. Cost-effectiveness analysis of adjuvant therapy with trastuzumab (Herceptin) for early breast cancer. Ann Oncol 2006; 17: ix95.

13. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983; 3: 419–458.

14. Drummond MF, Sculpher MJ, Torrance GW et al. Methods of the Economic Evaluation of Health Care Programmes. Oxford, UK: Oxford University Press 2005.

15. Swiss Federal Office of Statistics. Mortality Rates. http://www.bfs.admin.ch (12 November 2007, date last accessed).

16. Shen J, Hunt KK, Mirza NQ et al. Predictors of systemic recurrence and disease-specific survival after ipsilateral breast tumor recurrence. Cancer 2005; 104: 479–490.

17. Harris EE, Hwang WT, Seyednejad F, Solin LJ. Prognosis after regional lymph node recurrence in patients with stage I-II breast carcinoma treated with breast conservation therapy. Cancer 2003; 98: 2144–2151.

18. Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087–2106.

19. National Institute for Health and Clinical Excellence. http://www.nice.org.uk (12 November 2007, date last accessed).

20. Smith I, Procter M, Gelber RD et al. Improved survival with trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. Lancet 2006; 369: 29–36.

21. Ewer MS, Vooletich MT, Durand JB et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005; 23: 7820–7826.

22. Schweizerische Arzneimittelkompendium. http://www.documed.ch (12 November 2007, date last accessed).

23. Tarmed Suisse. http://www.tarmed.org (12 November 2007, date last accessed).

24. Norum J, Risberg T, Olsen JA. A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a model-based cost-effectiveness analysis. Ann Oncol 2005; 16: 909–914.

25. Ess SM, Luscher TF, Szucs TD. High dose lisinopril in heart failure: economic considerations. Cardiovasc Drugs Ther 2002; 16: 365–371.

26. Thurlimann B, Keshaviah A, Coates AS et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005; 353: 2747–2757.

27. Bendell JC, Domchek SM, Burstein HJ et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97: 2972–2977.

28. Moliterni A, Menard S, Valagussa P et al. HER2 overexpression and doxorubicin in adjuvant chemotherapy for resectable breast cancer. J Clin Oncol 2003; 21: 458–462.

29. Paik S, Bryant J, Tan-Chiu E et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: national surgical adjuvant breast and bowel project protocol B-15. J Natl Cancer Inst 2000; 92: 1991–1998.

30. Eichler HG, Kong SX, Gerth WC et al. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004; 7: 518–528.

31. Tengs TO, Adams ME, Pliskin JS et al. Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal 1995; 15: 369–390.

32. Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer 2004; 101: 1311–1322.

33. Cameron DA, Geyer CE, Chan DS et al. Lapatinib in combination with capecitabine demonstrates superior efficacy compared with capecitabine alone in ERBB2+ advances or metastatic breast cancer patients pretreated with chemotherapy and trastuzumab. Ann Oncol 2006; 17: ix69.