International Journal of Technology Assessment in Health Care, **21:1** (2005), 132–137.

Cost-effectiveness of Herceptin®: A standard cost model for breast-cancer treatment in a Belgian university hospital

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Objectives: The objective of this study was to conduct a cost-effectiveness analysis of Herceptin® from the hospital's point of view. This new biotechnological pharmaceutical is a humanized monoclonal antibody that targets the HER2 receptor, an important anti-cancer target.
Methods: A cost model with standard diagnostic and treatment options for breast cancer was set up for a Belgian university hospital in close collaboration with its specialists. Direct and indirect costs were calculated for each diagnostic and treatment option using the micro-costing method. Effectiveness was estimated through a literature study. The model allowed us to take cost consequences in other stages of the model into account and to calculate changes in monthly treatment costs from different "starting points." With an incremental cost-effectiveness analysis, differences in costs and effectiveness with and without Herceptin® were compared.
Results: Over the complete treatment period from diagnosis until the metastatic phase, monthly costs for the hospital rose from €85.07 to €90.35 for stage I diagnosed breast cancer when adding Herceptin® to the model. In the metastatic phase alone, these costs rose from €1,132.33 to €1,256.23. With Herceptin®, we found an extra cost of €3,981.44 per extra life-month.
Conclusions: This cost-effectiveness ratio was rather high, because Herceptin® was quite expensive and the product was additive in its current use and did not replace existing treatments. Future research will concentrate on alternative applications of Herceptin® based on ongoing Herceptin® trials and expert opinions.

Keywords: Herceptin®, Breast cancer, Monthly costs, Incremental cost-effectiveness ratio

Pressures on health-care budgets have forced pharmaceutical companies to generate evidence on whether the use of their products creates value for money. In Australia and Ontario, governments require cost-effectiveness evidence of new products for decisions on reimbursement. As early as in 1990, Australia drafted guidelines for this type of economic analysis, which have had to be followed since 1993 (5). Many other countries are discussing the use of economic evaluation of pharmaceuticals. A study by Nuijten (8) points to the growing impact of health economic data to support pricing and reimbursement decisions.

The process of developing a standard breast-cancer treatment model required input from numerous persons. The authors wish to acknowledge the support of the staff of Ghent University Hospital, the peripheral hospitals Sint-Lucas (Assebroek) and Sint-Jan (Brugge), and Roche for their cooperation.

Each author contributed to both the conception/design and/or analysis/interpretation of the project and the writing of the paper. Each has approved the version being submitted, and the content has not been published nor is being considered for publication elsewhere.

This study demonstrates that a pharmacoeconomic analysis provides essential information for decision-makers. A cost-effectiveness analysis has been carried out for Herceptin®, a new biotechnological pharmaceutical developed by Genentech. Herceptin® is a humanized monoclonal antibody that targets the human epidermal growth factor receptor-2 (HER2), an important anti-cancer target. The HER2 receptor is considered to be an important mediator of cell growth, differentiation, and survival (10). HER2 overexpression occurs in 25 percent to 30 percent of human breast cancers (1). In this study, calculations were made on the assumption that 30 percent of the population could be treated with Herceptin.

In September 1998, Herceptin® was approved by the U.S. Food and Drug Administration (FDA) for the treatment of women with HER2-positive metastatic breast cancer, both as a first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy. In Belgium, Herceptin® has been registered as single agent therapy or in combination with paclitaxel. Reimbursement is only approved for Herceptin® as single agent after the failure of two previous treatments with chemotherapy, in which at least one anthracycline and one taxane were used. HER2 overexpression also has to be proven by a FISH (fluorescence in situ hybridization) test (9).

The future use of Herceptin® among other things will depend on the outcomes of the ongoing Herceptin® Adjuvant Trial (HERA) and BCIRG 006 trials. These important international studies aim to evaluate the effectiveness of adjuvant Herceptin® treatment in HER2-positive patients with primary breast cancer. Our cost-effectiveness analysis of Herceptin® is based on the actual use of the product for metastatic breast cancer.

METHODS

Standard Costs

Herceptin® treatment involved indirect costs and had an influence on costs made in earlier phases of the breast-cancer treatment. An economic evaluation without detailed cost information cannot provide reliable results. Unfortunately, detailed real cost data for a complete breast-cancer treatment scheme are not available in Belgium. Charges are rather easy to find but real costs for hospitals are not necessarily equal to what they receive for a specific treatment. Even a consistent relation between hospital charges to patients for products or services and the actual costs of those products or services does not exist (4). We have opted, therefore, to work with real costs for the average patient or standard costs. This approach is not only reliable but also yields results that will not be influenced by administrative decisions that impact on how much hospitals can charge for specific treatments. This method required close collaboration with an experienced and representative treatment center.

Cost Model

The costs were calculated from the perspective of the hospital or the care provider. We cooperated with a university hospital, located in Flanders, the northern part of Belgium. In this study, we present the standard diagnostic and treatment model of the university hospital. All data were drawn up, put together, and checked in close collaboration with specialists of this hospital during 2002–2003.

When assessing the impact of Herceptin®, it is essential to compare total treatment costs with and without Herceptin®. Herceptin® was only used in the metastatic treatment phase in our university hospital (Figure 1B). The treatment was supplementary and did not replace other treatments.

We set up the treatment model (Figure 1A) starting from diagnosis until the metastatic phase for several reasons. First, the use of Herceptin® had consequences in an earlier stage of the model. To see whether treatment with Herceptin® could be effective, HER2 overexpression had to be proven by a FISH test. There were other tests possible, but this test was necessary to qualify for reimbursement in Belgium. Because Herceptin® was later used in a much smaller group of patients with HER2 overexpression, the costs of the test could not simply be added up to calculate the total standard costs. In addition to calculating monthly treatment costs for using Herceptin®, we considered it useful to know the cost consequences of using this product for the metastatic phase or for the total standard treatment costs. Therefore, different "starting points" were used in our analysis, that is, diagnosis confirms breast cancer, the metastatic phase, and the moment Herceptin® is administered.

Micro-Costing

For each phase of the model, the standard diagnostic and treatment options were taken into account. Once these different types of options were defined, costs were calculated. The main direct cost-drivers were the use of personnel, medication, materials, equipment, and the costs for the stay in hospital. Indirect costs made for preparing medication, sterilizing materials, and maintaining apparatus were also taken into account, because they were related to the specific treatment options. Costs caused by complications were not interpreted as standard costs and, therefore, were not taken into account. Overhead costs and costs linked to research activities were also disregarded, because they are in the first place related to a specific department and not to a specific diagnostic or treatment option. In other words, the real costs were higher than our calculated standard costs and they only reflected a part of total department expenditures.

The personnel, medication, materials, and equipment costs were calculated directly by using the *bottom-up* or *micro-costing* method in which the costs were calculated by directly tracing resources. The personnel costs were estimated by multiplying the time different people were

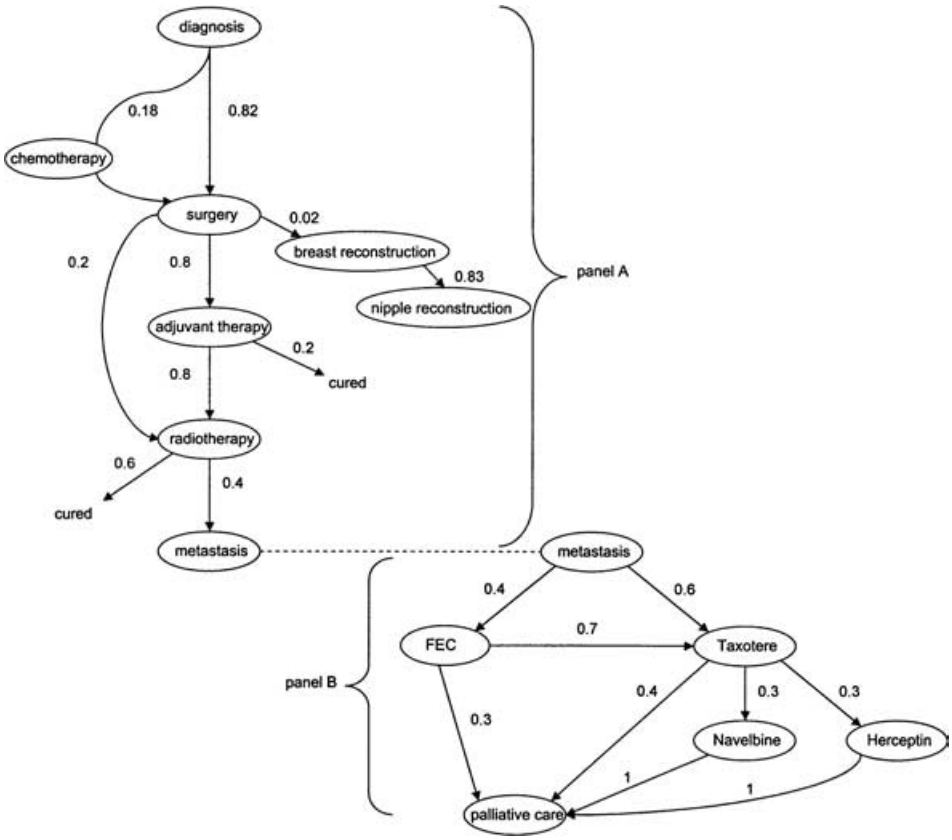

Figure 1. Standard breast-cancer treatment model in a Belgian university hospital.

involved by their average labor cost. The costs of medication and disposable materials were based on the standard amounts used, multiplied by their unit prices. The costs for reusable materials were divided by the number of times they were reused. Equipment costs consisted of acquisition and maintenance costs. Acquisition costs were distributed over the estimated number of years during which an apparatus would be used. This amount was then divided by the estimated number of times a year the equipment was used. If the equipment was used for different purposes, the number of hours used was taken as a distributive key. Maintenance costs were also taken into account. Other cost-drivers such as the costs made by the pharmacy for preparing medication, anesthetic costs, costs for sterilizing instruments, laboratory costs for investigating the cancer before treatment was started, and checking the blood image before medication was administered, were also taken into account with the micro-costing method.

The costs for staying in hospital were estimated indirectly by a *top-down* calculation. We started by subdividing the hospital-stay price into its different components. To avoid double counting, we adjusted this hospital-stay price by subtracting those parts already taken into account in a direct way. For example, depreciation costs of medical equipment represented a certain amount in total hospital-stay price. Because these costs were already calculated for each diagnostic or treatment option through micro-costing, we adjusted the hospital-stay price for this amount.

Finally, the follow-up costs were also considered. The costs for the different follow-up investigations were also calculated with the micro-costing method.

The average costs for each phase in the treatment model were calculated by multiplying the cost of each diagnostic or treatment option by its ratio of use, which reflected the chance that a certain option was carried out. The costs for the complete model were estimated by using flow through ratios, which showed how many patients on average went from one phase in the model to another phase. Follow-up costs and laboratory costs were finally added to become total costs. Where possible, the ratios of use and flow-through ratios were based on databases of the university hospital. If such a database did not exist, we relied on information of the university experts based on their knowledge and perception of the current treatment and diagnostic options used in their department.

Results from the Cost Model

Table 1 presents the end results of our micro-costing calculations of standard direct and indirect costs. The diagnostic

https://doi.org/10.1017/S0266462305050178 Published online by Cambridge University Press

Table 1. Standard Costs

Diagnosis	€77.02
Preoperative chemotherapy	€1,796.16
Breast surgery	€2,102.90
Breast reconstruction	€4,395.17
Nipple reconstruction	€217.82
Adjuvant therapy	€3,375.03
Radiotherapy	€1,278.86
Metastasis	
Without Herceptin®	€19,852.04
With Herceptin®	€22,500.59
Laboratory	
Coloring test	€146.05
FISH test	€196.82
Blood test	€32.62
Basic check up	€13
Mammography and ultrasound scan	€59.41
Bone scan	€73.50
Ultrasound scan liver	€12.81
X-ray thorax	€25.04
Anesthesia	
Start-up	€81.30
Maintenance	€38.13/hour
Pharmacy	€15.60
Sterilization	€12.38/cycle
Hospitalization	€303.85/day

FISH, fluorescence in situ hybridization.

phase included costs of radiology and biopsy. If breast cancer was diagnosed, approximately 18 percent of patients received preoperative chemotherapy (see Figure 1). The initial breast surgery could be a lumpectomy or mastectomy as such or in combination with the removal of the axillary nodes or a sentinel procedure. Depending on the results of the latter procedure, the axillary nodes could be removed. After mastectomy, which was performed in approximately 30 percent of all cases, 5 to 10 percent of patients had a breast reconstruction. In our university hospital, a DIEP or GAP flap was used. Of this group, 80 to 85 percent had a nipple reconstruction, which consisted of the reconstruction and coloring the reconstructed nipple and areola. After surgery, hormone therapy and/or chemotherapy could be given and could be followed by radiotherapy. To keep the presentation brief, the flow-through ratios (Figure 1A) and standard costs per phase (Table 1) are consolidated numbers. We have presented the metastatic phase more in detail (Figure 1B), because we want to compare treatment costs with and without Herceptin®. The costs of the metastatic phase were calculated both with and without this additional treatment.

During breast-cancer treatment some laboratory examinations were carried out. First, after the presence of a malignancy was confirmed, a tissue examination was used to select further treatment. We refer to this test as the "coloring test." Second, one of the conditions for reimbursement in Belgium was that the HER2 overexpression had to be proven by a FISH test. Finally, during follow-up and before administering chemotherapy, a blood test was performed. The follow-up procedure consisted of different examinations performed at several points in time. In addition to the basic check-up, blood test, mammography and ultrasound scan, also included were a bone scan, an ultrasound scan of the liver, and an X-ray of the thorax.

Some costs that had an influence on some of the previously mentioned costs were calculated separately. Anesthesia costs consisted of the start-up costs and increased for each hour the anesthesia was maintained. Pharmacy costs for preparing the administered chemotherapy were also calculated separately. Sterilization costs for reusable materials were calculated per cycle and divided by the number of sets or instruments made sterile per cycle. Finally, the hospital-stay costs were also calculated separately.

Table 2 presents the calculated total average costs for treatment of breast cancer in our university hospital. This value was the sum of the costs made during the different phases of the treatment model and the additional laboratory and follow-up costs. Only costs during the terminal palliative phase were not included, because this type of care strongly varied from patient to patient. Consequently, it was not possible to set up a standard treatment scheme for this phase in our university hospital. A distinction was made, depending on the point of time in the model and on whether or not Herceptin® was included. With Herceptin®, a distinction was made on whether or not the cost of the FISH test was taken into account.

Effectiveness

We conducted a literature review to assess the medical effectiveness of breast-cancer treatments and treatment with Herceptin®. Berkowitz et al. (2) found that life expectancy at diagnosis was 16.9 years for stage I breast cancer. They also reported that the average duration between the initial diagnosis of breast cancer and the progression to metastatic disease was 10.2 years for stage I disease. A study of Honig (6) reported that the median survival time for the metastatic phase was 18 to 24 months. Furthermore, a study of Cobleigh et al. (3) concluded that prolongation of life due to the use of Herceptin® in a metastatic setting was 3.1 months. Finally, studies of Berkowitz et al. (2) and Will et al. (11) considered the last 3 months before death as the terminal phase of breast-cancer patients.

Table 2. Total Standard Costs

Starting point	Before Herceptin®	With Herceptin®	
		Without FISH	With FISH
Diagnosis confirms breast cancer	€17,252.69	€18,150.70	€18,347.52
Metastatic phase	€20,381.86	€23,054.50	€23,640.28
Taking Herceptin®	€0.00	€10,123.63	€12,342.48

FISH, fluorescence in situ hybridization.

https://doi.org/10.1017/S0266462305050178 Published online by Cambridge University Press

On the basis of these data, we calculated average lifetime before and with the use of Herceptin®. A distinction was made on the basis of whether or not patients progressed to metastatic breast cancer. For the group progressing to metastatic disease, lifetime was estimated for the different starting points in the model. First, we look at the group of patients in which the disease becomes metastatic. Before Herceptin® was used, the metastatic phase with exclusion of the terminal phase lasted 18 months. This time was the average time between metastatic breast cancer and death minus the last three terminal months. The terminal phase was not included, because costs and effects had to be related to each other and the costs for this phase were not included in this study. The average duration between the initial diagnosis of breast cancer and the progression to metastatic disease for stage I breast cancer, which was 122.4 months, was added up to these 18 months to determine the estimated lifetime from the moment of diagnosis, which was 140.4 months. For all patients, life expectancy at diagnosis was 16.9 years (2) or 202.8 months before the use of Herceptin®. With the two previous data and knowing that, in our study, 33.6 percent of patients progressed to metastatic breast cancer, we were able to calculate the estimated lifetime of patients for which breast cancer did not become metastatic. This time was 234.38 months, and this number was not influenced by the use of Herceptin®, because the product was only administered in the metastatic setting.

With the use of Herceptin®, the delay in time to progression had to be taken into account. With taking Herceptin® as the starting point of the analysis, the average lifetime without inclusion of the terminal phase was 3.1 months. With 26.4 percent of people in metastatic phase treated with Herceptin®, we found an estimated lifetime for the metastatic phase of 18.82 months. Adding the average duration between the initial diagnosis of breast cancer and the progression to metastatic disease gave us an estimated lifetime of 141.22 months. With the calculated lifetime for patients where the disease, respectively, did or did not become metastatic and with a flow-through ratio to metastatic disease of 33.6 percent, we found a calculated lifetime of 203.08 months for all patients.

Economic Evaluation

Table 3 presents the estimated average monthly costs for breast-cancer treatment in our university hospital. These numbers were obtained by dividing estimated total average treatment costs (Table 2) by estimated lifetime. We did this for different starting points in our model. It was clear that the closer to palliative care, the higher monthly expenses were. Next to different starting points, we also made a distinction as to whether Herceptin® was administered or not. If administered, we made a further distinction on whether or not the FISH test was taken into account.

Because Herceptin® treatment did not replace other treatment options, estimated average monthly treatment costs rose. When comparing the situations of whether or not including Herceptin® in the model, the costs were very obvious with Herceptin® as starting point of the analysis. These costs amounted to approximately €4,000 monthly. Instead of just looking at this final stage, it was more interesting to look at the results for the metastatic phase or the entire breast-cancer treatment model. When looking at the complete breast-cancer treatment, starting from diagnosis, monthly treatment costs increased more than 6 percent from €85.07 to €90.35 because of adding Herceptin® to the treatment model. In the metastatic phase, these costs rose by approximately 11 percent from €1,132.33 to €1,256.23.

Table 3. Estimated Average Monthly Costs for Breast-Cancer Treatment

Starting point	Before Herceptin®	With Herceptin®	
		Without FISH	With FISH
Diagnosis confirms breast cancer	€85.07	€89.38	€90.35
Metastatic phase	€1,132.33	€1,225.10	€1,256.23
Taking Herceptin®	/	€3,265.69	€3,981.44

FISH, fluorescence in situ hybridization.

The incremental cost-effectiveness ratio was calculated by taking the difference between total costs for treatments of breast cancer with and without Herceptin® (Table 2) and dividing this number by the difference in estimated lifetime with or without Herceptin®. The result was the same for all starting points because, once a certain point in the model was selected to calculate the incremental ratio, the percentage of patients influencing costs and effectiveness was the same, that is, the percentage of people treated with Herceptin®. Because numerator and denominator of the ratio would be influenced in the same order, the incremental cost-effectiveness ratio would not vary along with the chosen starting point. The incremental cost was €3,981.44 per month when taking the FISH test into account.

The impact on monthly costs of not taking up the costs for the FISH test was maybe not so clear when looking at diagnosis as the starting point of the analysis, because the costs were spread over a higher number of months. But the shorter the remaining lifetime, the clearer it was that these extra costs should not be omitted, especially because the cost of this HER2 overexpression test, which all patients received, had to be allocated to the group of patients actually treated with Herceptin®. When looking at the final stage where Herceptin® was taken, the FISH test accounted for an extra cost of approximately €715 per month.

CONCLUSIONS

In this study, a cost model for breast-cancer treatments in a Belgian university hospital was set up. We estimated costs from the hospital's point of view, using the micro-costing

https://doi.org/10.1017/S0266462305050178 Published online by Cambridge University Press

method. This strategy was necessary because what hospitals charge differs from real costs. Only the hospital-stay costs were estimated indirectly using the hospital-stay price, which was adjusted to avoid double counting.

In our economic evaluation, based on our cost model, we estimated the influence of Herceptin® on the monthly standard costs for breast-cancer treatment. It was essential to mention the time period considered in the evaluation. When looking at the period starting from diagnosis and ending in the metastatic phase, costs rose from €85.07 to €90.35 per month when adding Herceptin® treatment to the model. When only considering the metastatic phase, monthly costs rose from €1,132.33 to €1,256.23.

The incremental cost-effectiveness ratio was strongly influenced by the cost of the FISH test. Instead of €3,265.69 per extra life-month, €3,981.44 was a more precise calculation of this extra life-month cost. In addition to the price of the product, that Herceptin® did not replace other treatment options made these costs rather high.

POLICY IMPLICATIONS

In its current use, Herceptin® has a high cost-effectiveness ratio. When used in new applications and settings, it is essential to perform new cost-effectiveness studies of this product. This approach can eventually support decision making during further technology development before the product is widely spread (7). In further research, several alternatives for the future use of Herceptin® based on the HERA and BCIRG 006 trials and expert opinions will be evaluated and compared with the existing situation. These studies are needed to assess budget implications and to measure the product's value for money in its future applications.

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