Cost-effectiveness analysis of breast cancer adjuvant treatment: FEC 50 versus FEC 100 (FASG05 study)

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Received 29 June 2004; revised 20 September 2004 and 24 December 2004; accepted 20 January 2005
Published online 13 May 2005

Background: The aim of the study was to assess the incremental cost-effectiveness ratio (ICER) of the FEC 100 compared with the FEC 50 in the FASG05 trial.

Materials and methods: A cost-effectiveness analysis was performed using a multi-state Markov process model. Relevant clinical data introduced into the model were obtained from 10-year follow-up of the clinical trial FASG05. Survival curves for each health state were assessed by survival parametric model. The model allowed assessments from the start of adjuvant chemotherapy until death. The costs of adjuvant treatment and follow-up were estimated. The costs of recurrence were evaluated from the medical records of 146 patients. A prospective survey was performed on a cohort of 87 patients to quantify the resources external to the hospital (including cost of transportation). The inpatient costs were evaluated using the French diagnosis-related groups. The ambulatory costs were assessed using the French nomenclature. Costs were expressed in 2002 Euro (€), according to the French societal perspective. The ICER assessed the cost of one additional life year saved. A discount rate of 5% per year was used for cost, and alternatively 0%, 3% and 5% for effectiveness. We validated the results with a probabilistic sensitivity analysis incorporating parametric and non-parametric bootstraps, and with the acceptability curves.

Results: The mean total discounting cost of adjuvant treatments was 11 465€ for FEC 50 and 13 815€ for FEC 100; the mean total discounting cost of recurrences was 14 636€ and 13 503€, respectively. According to the discount rate of effectiveness, the life expectancy was 16.5, 11.4 and 9.3 years for FEC 50 and 18.4, 12.5 and 10.2 years for FEC 100. The ICER (cost per life year saved) were 642€, 1084€ and 1460€, respectively. The probability according to which FEC 50 is strictly dominated by FEC 100 was 0.15.

Conclusion: The clinical benefit of FEC 100 generates a negligible cost increase when compared with FEC 50.

Key words: adjuvant, breast cancer, cost, cost-effectiveness, FEC

Introduction

Breast cancer is the most frequent tumor in females in the western world, with a lifelong risk of about one out of eight to 10 [1]. Breast cancer treatment generally combines surgery, radiation therapy, hormone therapy in hormone-sensitive tumors and chemotherapy. Adjuvant chemotherapy has been recommended at several consensus conferences. Although the recommendations are not entirely identical, adjuvant chemotherapy is frequently used. Its benefit is modest but highly significant, as described in the meta-analysis published in The Lancet [2]. Short- and long-term toxicities may nevertheless be high, as well as the cost of these treatments. Therefore, the cost–benefit ratio of adjuvant chemotherapy needs to be investigated.

There is no unique ‘reference’ protocol for adjuvant chemotherapy. The FEC 50 protocol is nevertheless considered to be more effective than CMF-like regimens [3]. Moreover, the FEC 100 regimen is associated with a higher disease-free survival and overall survival than FEC 50 [4], the two protocols differing only in the epirubicin dose, which is respectively 100 and 50 mg/m². These results on disease-free and overall survival rates have also been confirmed after a median follow-up duration of 10 years [5]. Only one case of myeloblastic leukemia was observed and long-term cardiotoxicity was extensively studied on a subpopulation of patients who had not relapsed after a minimum follow-up duration of 5 years [6]. To our knowledge, no health-economic/pharmaco-economic study
on FEC 100 has been published so far. The aim of this study was to assess the incremental cost effectiveness ratio (ICER) of FEC 100 regimen given as adjuvant treatment of breast cancer when compared with FEC 50.

Patients and methods

Patients

Patients included in the analysis were those included in the clinical trial comparing FEC 50 and FEC 100 (FASG05).

A total of 565 patients aged <65 years with more than three positive axillary nodes, or between one and three but with another poor prognostic factor (tumor diameter >3 cm, histoprognostic grade III, no estradiol nor progesterone receptor), were randomized after curative surgery between FEC 50 (fluorouracil 500 mg/m², cyclophosphamide 500 mg/m² and epirubicin 50 mg/m²) and FEC 100 (epirubicin 100 mg/m² and the same dose for the two other drugs) for six cycles [4].

Two former independent studies were also included in the analysis to estimate outpatient costs and the cost of relapse.

Outpatient costs were assessed by a study based on the interview of 87 consecutive patients receiving adjuvant chemotherapy for breast cancer as outpatients in the Centre Oscar Lambret. These patients were asked about their medical expenses outside of the hospital during the last 4 months (visits to a general practitioner, a nurse, radiographs, biological determinations, etc.) [7].

The medical files of 146 patients whose first relapse occurred between 1983 and 1990 were reviewed to estimate the cost of relapse. A metastatic disease was the first relapse in 99 of them. The other 47 patients had a local relapse. All the patients had at least a 5-year follow-up since the initial diagnosis. For those patients with local relapse only, a follow-up duration of at least 5 years after relapse was mandatory in order not to rule out a disseminated disease in the years following the local relapse [8, 9].

Model

All the patients from the FASG05 study have been analyzed using a Markov model. The model allows a representation of the different possible outcomes for a patient, from the beginning of the adjuvant treatment until death (Markov process) using the FASG05 patient database. The number of events and transition from one health state to another can thus be deduced for each strategy. The range of time has been divided into 6-month periods because of the duration of adjuvant treatment (minimum 18 weeks). The rationale for the 6-month period was for all the chemotherapy cycles to be included in the first period.

The structure of the Markov model is showed in the Figure 1. Three transition health states were defined: ‘good functional state’ (the patient is still alive, free of recurrence after six cycles of chemotherapy), ‘local recurrence’ and ‘metastatic recurrence’; and one absorbing state: ‘death’.

Based on the clinical data, a multi-state model can be elaborated in order to take into account the available information and estimate survival over 10 years [9–11].

The probabilities of survival in each health state were estimated by fitting a parametric survival distribution to the estimated survival curves, whereby these may be extrapolated to converge with the x-axis, to the point where the survival function \( S(t) = 0 \) is equal to zero. Many different parametric distributions can be used. The distribution used in the model was the generalized gamma distribution. The generalized gamma distribution includes other distributions as special cases based on the values of the three parameters (exponential, log-normal and gamma) allowing a better adjustment to the observed clinical data. The generalized gamma density function is written:

\[
 f(t) = \frac{\beta}{\Gamma(k)} \left( \frac{1}{\beta} \right)^{k-1} \exp\left( -\left( \frac{t}{\beta} \right)^k \right)
\]

where \( \theta > 0 \) is the scale parameter and \( \beta > 0 \) and \( k > 0 \) are the shape parameters and \( \Gamma(x) \) is the gamma function \( \Gamma(x) = \int_0^\infty e^{-u}u^{x-1}du \).

The survival function also estimated, the probability at 6 months to be in the same health state is equal to \( \frac{S(6)}{S(6)+D} \).

Costs evaluation

The costs of adjuvant therapy can be split into two parts: the costs of treatment and follow-up and the costs of relapse. In this study, only direct costs (medical and non-medical) were considered.

The economic perspective of the study

The most appropriate approach is the broadest perspective, i.e. the French societal perspective using the diagnostic-related group (DRG) in a way that allows the inclusion of the cost of epirubicin.

The mean total cost and the mean value for each type of cost (acquisition of drugs, radiological tests, physician and nurse work, logistics, etc.) are described for every DRG. The method identifies the DRGs corresponding to outpatient hospitalization for the administration of adjuvant chemotherapy and integrates in these DRGs the costs of treatment (FEC 50 or FEC 100).

Cost of adjuvant treatment and patient follow-up

Unit costs. The following items were considered as medical costs:

(i) Hospital costs: postoperative radiation therapy; patient follow-up (mammography and specialist visits); and adjuvant treatment.

(ii) Ambulatory costs: visits at the referring physician; nurse care; physical therapy; and hematological and radiological exams.

The cost of patient transportation from home to the hospital was the only direct non-medical cost to be considered.

Unit costs are presented in Table 1.

Health care resources data sources. The management of a patient treated for breast cancer was described by experts from the Centre Oscar Lambret as follows: the adjuvant treatment was administered every 3 weeks in outpatient status. A blood test was performed out of the hospital the day before chemotherapy. Patient transportation was considered within the cost of the adjuvant strategy. The follow-up included two visits per year.

\[ \text{Figure 1. The Markov model.} \]
with the specialist during the first 5 years, and one visit per year during the following 5 years. One mammography was performed every year. Prevention of adverse events was also described as follows: the prevention of FEC 50-induced nausea and vomiting was performed using intravenous anti-5HT3 and 80 mg glucocorticoids. For FEC 100, the dose of glucocorticoids was increased to 120 mg; two tablets of oral 5HT3 inhibitor per day for 3 days were added. The cost of antiemetics for FEC 50 and FEC 100 were 31.97 € and 127.31 €, respectively.

The cost of small equipment (e.g. single use equipment such as needles, syringes, saline, etc.) necessary for the administration of chemotherapy was estimated to be 19.8 € in a previous study [8].

Cost of recurrence. The cost evaluation of the treatment strategy for patients with recurrence was based on a previous study and updated using a DRG approach.

This database gave the following information: number of visits with the specialist, number of inpatient and outpatient hospitalizations, information regarding radiation therapy (French nomenclature), number of transportations to the hospital and the average distance in kilometers to the hospital, number of biological and radiological exams for follow-up according to the type of recurrence, and the costs of ambulatory treatment.

The costs of hospitalization for metastases were estimated using the DRG. The cost of the various DRGs is weighted by the type of metastasis (cerebral, bone, chest, etc.) according to the FASG05 database.

Incremental cost-effectiveness

The purpose of this cost-effectiveness analysis is to evaluate the cost to consent in order to obtain a clinical benefit when using FEC 100 instead of FEC 50 in the FASG05 trial.

A discount rate of 5% per year was used for costs, and 0%, 3% and 5% for effectiveness.

The effectiveness with a discount rate of 0% corresponds to the estimated life expectancy without any discounting of the cohort FEC 100 or FEC 50 patients, according to the results of the FASG05 study.

Sensitivity analysis

We conducted a probabilistic sensitivity analysis using a Bayesian second-order Monte Carlo simulation to evaluate the uncertainty in the assumptions and to model the distribution of effectiveness and costs. A probability distribution was assigned to all estimates and assumptions that are not fixed values in order to capture the possible range of outcomes. After the probability distributions were assigned, the simulation drew one value at a time from the feasible range simultaneously for each parameter. The cost and benefit were then calculated from the specific values of the input parameters. This process was repeated 100,000 times, resulting in 100,000 unique estimates of effectiveness and costs, generating a range of possible values.

Probability distributions were selected based on the expected distributions of the underlying parameters for transition probabilities, hospital costs and resource utilization. Probabilities were assumed to follow a beta distribution to reflect the normal distribution and restriction to values between zero and one. Mean hospital costs were expected to follow a triangular distribution, reflecting the long right tail and restriction to positive values according to the cost data in the French DRG (minimal, maximal and mean costs). Mean resources utilization costs were expected to follow a simulated multivariate distribution estimated by non-parametric bootstrapping method using Monte Carlo simulation for 10,000 sets of input parameters were randomly sampled.

Results

The overall survival of patients treated with FEC 50 and FEC 100 were estimated using the Markov process.
Costs of the adjuvant treatment and its follow-up

The costs of the various adjuvant strategies after 10 years per patient without recurrence are presented in Table 2. Regarding the acquisition and the administration of treatment, the costs of one administration of FEC 50 and of FEC 100 were 652€ (416€–1388€) and 1013€ (776€–1748€), respectively. The difference was essentially due to the acquisition cost of epirubicin and less to the management of emesis. There was no difference in the other costs between the two strategies. The costs of follow-up from years 2–5 and years 6–10 were 609€ and 485€, respectively.

In total, after 10 years, the discount acquisition, administration and follow-up costs for each patient without recurrence receiving FEC 50 was 13 020€ (11 600€–17 433€), and 15 182€ (13 762€–19 595€) for those receiving FEC 100.

Cost of recurrence

The costs of local and metastatic recurrence per patient are shown respectively in Table 3.

After 10 years, the total discount cost of local recurrence was 21 236€ (9939€–53 338€). Over half of the cost appears during the first year of local recurrence.

### Table 2. Costs of adjuvant treatment and follow-up per patient without recurrence

<table>
<thead>
<tr>
<th>Costs of acquisition and administration of treatment</th>
<th>Year 1</th>
<th>Years 2–5</th>
<th>Years 6–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHM 681 without drug cost</td>
<td>312.64€/6 cycles = 1876€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil (500 mg/m²)</td>
<td>4€/6 cycles = 24€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin (50 mg/m²)</td>
<td>265€/6 cycles = 1590€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin (100 mg/m²)</td>
<td>530€/6 cycles = 3180€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (500 mg/m²)</td>
<td>10€/6 cycles = 60€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>28.62€/6 cycles = 172€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiemetics FEC 50</td>
<td>31.97€/6 cycles = 192€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiemetics FEC 100</td>
<td>127.31€/6 cycles = 764€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost for FEC 50</td>
<td>652.23€/6 cycles = 3913€ (2493.39–8326.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost for FEC 100</td>
<td>1012.57€/6 cycles = 6075€ (4655.43–10 488.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual other costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood tests (10.80€)</td>
<td>65€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (66.50€)</td>
<td>1596€</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits (22.87€)</td>
<td>46€</td>
<td>46€</td>
<td>23€</td>
</tr>
<tr>
<td>External costs (360.27€)</td>
<td>360€</td>
<td>360€</td>
<td>360€</td>
</tr>
<tr>
<td>Transportation (101.68€)</td>
<td>3152€</td>
<td>203€</td>
<td>102€</td>
</tr>
<tr>
<td>Total other costs</td>
<td>5219€</td>
<td>609€</td>
<td>485€</td>
</tr>
<tr>
<td>Total cost for FEC 50b</td>
<td>9132€</td>
<td>11 570€</td>
<td>13 994€</td>
</tr>
<tr>
<td>Total cost for FEC 100b</td>
<td>11 294€</td>
<td>13 732€</td>
<td>16 156€</td>
</tr>
</tbody>
</table>

^aMean (range).

^bNot discounted.

### Table 3. Costs (in €) of local recurrence and metastasis

<table>
<thead>
<tr>
<th>Local recurrence (cost in €)</th>
<th>Metastasis (cost in €)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>At 5 years</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Physician visit</td>
<td>72</td>
</tr>
<tr>
<td>Outpatient</td>
<td>865</td>
</tr>
<tr>
<td>Inpatient</td>
<td>8407</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>245</td>
</tr>
<tr>
<td>Transportation</td>
<td>1205</td>
</tr>
<tr>
<td>Ambulatory treatment</td>
<td>269</td>
</tr>
<tr>
<td>Medical assessment</td>
<td>587</td>
</tr>
<tr>
<td>Mean total cost</td>
<td>11 650</td>
</tr>
</tbody>
</table>

Discount rate of 5%.
Cost-effectiveness results

According to the hypotheses, the life expectancy without discounting with FEC 100 was 18.4 years, 12.5 years with a 3% discount rate and 10.2 years with a 5% discount rate. With FEC 50, the life expectancy was 16.5, 11.4 and 9.3 years, respectively. The number of additional life years saved was then 1.9, 1.1 and 0.8 years.

Using a 5% discount rate, the acquisition, administration and follow-up costs for FEC 100 were €13 815, and for FEC 50 were €11 465.

The discount cost of local and metastatic recurrence was €13 503 for FEC 100 and €14 636 for FEC 50. The FEC 100 strategy was more costly regarding acquisition, administration of treatment and monitoring (difference of €2350), but less costly regarding the cost of recurrence (difference of €1134). The incremental cost was €1216.

The FEC 100 strategy was both more effective and slightly more expensive than the FEC 50 strategy. The incremental cost effectiveness ratio was respectively €642, €1084 and €1460 per life year saved for a discount rate, respectively, of 0%, 3% and 5%. However, it is not possible to calculate the standard deviation of the incremental cost-effectiveness ratio because of negative data to the denominator (Table 4).

Discussion

Our results show that the incremental cost per life year saved was €642 without any discount, €1084 with a 3% discount rate and €1460 with a 5% discount rate when patients were treated with FEC 100 instead of FEC 50. This incremental cost is very low when compared to the National Institute for Clinical Excellence proposals, which consider that £35 000 (∼€45 500) is an acceptable cost for a life year saved. The probabilistic sensitivity analysis allows the conclusion that the probability for FEC 100 to be strictly dominant was 15% (more effective and less expensive), the reverse being 4%. The acceptability curves show that the likelihood for the price to pay per life year saved to be less than the amount seen above was ∼41%. Long-term side effects are rare. Any cardiac toxicity is essentially asymptomatic, and in most cases not treated [5]. In our study, only one case of acute myeloblastic leukemia, which was probably related to chemotherapy, was observed. After 10 years of follow-up, it can be concluded that the cost between the two treatments is nearly identical with a significant number of life years saved for FEC 100.

Table 4. Cost-effectiveness results

<table>
<thead>
<tr>
<th>Discount rate:</th>
<th>Cost of adjuvant treatment in € (C) 5%</th>
<th>Cost of recurrences in € (B) 5%</th>
<th>Effectiveness in years (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%*</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Mean hypotheses: FEC 100</td>
<td>13 815</td>
<td>13 503</td>
<td>18.4</td>
</tr>
<tr>
<td>Mean (SD 95%)</td>
<td>13 815 (9775; 17 337)</td>
<td>13 503 (4747; 41 872)</td>
<td>16.5</td>
</tr>
<tr>
<td>Mean hypotheses: FEC 50</td>
<td>11 465</td>
<td>14 636</td>
<td>12.5</td>
</tr>
<tr>
<td>Mean (SD 95%)</td>
<td>11 466 (10 123; 14 838)</td>
<td>14 636 (5291; 45 755)</td>
<td>10.2</td>
</tr>
<tr>
<td>Mean hypotheses: ∆FEC 100 – FEC 50</td>
<td>2350</td>
<td>–1134</td>
<td>642</td>
</tr>
<tr>
<td>Mean (SD 95%)</td>
<td>2349 (–717; 2780)</td>
<td>–1134 (–5921; 2220)</td>
<td>0.8</td>
</tr>
<tr>
<td>∆(C–B)</td>
<td>1216</td>
<td>–3296; 3368</td>
<td>0.79</td>
</tr>
<tr>
<td>SD 95%</td>
<td>(–218 964)</td>
<td>1084/ per life year saved</td>
<td>79 (–0.34; 1.78)</td>
</tr>
<tr>
<td>ICER = ∆(C–B)/∆E</td>
<td>1460/ per life year saved</td>
<td>642/ per life year saved</td>
<td>1460/ per life year saved</td>
</tr>
</tbody>
</table>

The total cost of metastatic recurrence was 61 965€ (31 062€–218 964€). Over one-quarter of the cost appears during the first year of metastatic recurrence.

Sensitivity analysis

The results of the descriptive analysis of the probabilistic sensitivity analysis (mean and standard deviation) (Table 4) are extremely close to those obtained from the mean hypotheses (mean costs of DRG, external expenses and relapse and death probabilities). It allows to conclude that the number of simulations performed (100 000) was sufficient. Figures 2–4 show the plot of the 100 000 estimates of the ICER (∆C, ∆E) points on the incremental cost-effectiveness plane for the different
discount rate for effectiveness (0%, 3% and 5%). In terms of dominance of one strategy over another, the probability that FEC 100 strictly dominated FEC 50 (less costly and more effective) was 0.15, the probability to be strictly dominated (more costly and less effective) was 0.04.

Figure 5 presents the cost-effectiveness acceptability curve derived from the plot replicates in the (∆C, ∆E) planes corresponding to three different discount rates for effectiveness [12]. It shows, as a function of hypothetical threshold values of the decision maker’s willingness to accept an increase in costs, the proportion of the estimated ICER replicates that will be considered acceptable. Thus, if the critical threshold values are assumed to be equal to €642, €1084 and €1460, the probability that FEC 100 is cost-effective is equal to 42.2%, 41.9% and 41.8%, respectively. If the acceptable threshold is 10 000€, the probability is ∼90%.
The database for this study is sound. The clinical data of the 565 patients included in the FASG05 study were reviewed, with a median follow-up duration of 10 years; the number of events was very high in this poor prognosis patient population. Similarly, the consumed resources, either out of the hospital during the adjuvant treatment or after relapse, have been measured from the observation of important patient populations, using a questionnaire for the ambulatory study, or
Incremental effectiveness

Incremental costs

RCEI = 1460€

FEC 100 more costly and less effective than FEC 50
(p = 0.0395)

FEC 100 more costly and more effective than FEC 50
(p = 0.8102)

FEC 100 less costly and less effective than FEC 50
(p = 0.0052)

FEC 100 less costly and more effective than FEC 50
(p = 0.1451)

Figure 4. Incremental cost-effectiveness plane (discount rate for effectiveness 5%).

Cost-effectiveness acceptability curve (the probability that the incremental cost-effectiveness is <5000€ is <90%).
reviewing the clinical files of patients who relapsed. An advantage of the study is that it has been carried out in a well defined population of patients in whom the indication of adjuvant chemotherapy is not discussed according to the published consensus. The perspective of the study was the societal one, which is probably the most realistic approach that could be used. Very few studies have been published on the cost-effectiveness or cost-utility of adjuvant treatment in breast cancer. In addition, the methods that have been used are different, and thus the results difficult to compare. The incremental cost effectiveness of adjuvant CMF versus no treatment has been found to be US$447 (1€ is about US$1.2 in September 2004) per life year saved [13]; it is important to note that in Messori’s study, only the costs of chemotherapy administration were considered. Based on literature data incorporated with Norwegian standard adjuvant chemotherapy, Norum [14] found that the cost per life year saved was between £2365 and £6253, depending on the method used. Similarly, the cost per quality-adjusted life year saved was estimated to be between £2973 and £5737 (1€ is about £0.7 in September 2004). In Irvin et al.’s study [15], the ICE was estimated at US$1510 per life year saved with CMF and at US$1208 and US$1967, respectively, for stage II and III breast cancer patients. The cost of treatment and follow-up of breast cancer has been studied in a French group [16]; the mean cost was 10 072€, with extremes at 6384€ and 12 351€, depending on the treatments used; the median follow-up duration was 4 years and 4 months. When taking into account the differences between the costs that were considered and the methods of evaluation used, our results are very similar. In a worldwide evaluation of the cost of breast cancer, Radice et al. [17] found that the cost of initial care for stage I and II breast cancers are, respectively, US$10 835 and US$12 273, which is very similar to the previous one. The highest cost is for terminal care in patients with distant disease (about US$20 000). The 10-year cumulative cost per patient has been found to be 31 774€ in a Belgium group [18].

Based on our results, we can therefore conclude that the clinical benefit of FEC 100 generates a negligible cost increase when compared with FEC 50.

Acknowledgements
This study was supported by an unrestricted grant from Pfizer France.

References