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Cost Analysis Comparing an Anthracycline/Docetaxel Regimen to CMF in Patients with Early Stage Breast Cancer

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Key Words
Cost analysis · Docetaxel · Health resources · Breast neoplasm · Adjuvant chemotherapy

Summary
Background: Taxane-based adjuvant chemotherapy is the current standard for node-positive breast cancer patients. Recent data identified relevant patient subgroups with questionable benefit. To estimate the incremental burden on health care resources and costs, we compared a modern sequential regimen (4× epirubicin/cyclophosphamide; 4× docetaxel: EC→DOC) to CMF. **Patients and Methods:** Data were obtained alongside the phase III WSG-AGO Intergroup trial (2000–2005). A cohort of 110 patients receiving 1,047 chemotherapy cycle days at 38 study sites was analyzed from a hospital perspective. **Results:** Mean age was 52.4 years. Mean costs for the EC→DOC group (n = 54) totaled € 8,459 per patient (95% confidence interval (CI): € 7,785–9,132) with cytostatic drug costs being the largest burden (€ 5,673; 67%). CMF was significantly (–41.2%) less expensive (€ 4,973; 95% CI: € 4,706–5,240), and toxicity-associated rehospitalization was reduced by half (CMF: n = 4, EC→DOC: n = 8). **Conclusions:** Our results demonstrate a substantial budget increase attributable to introduction of taxanes to adjuvant chemotherapy of breast cancer. Data will allow estimating cost-effectiveness of individualized chemotherapy strategies.

Schlüsselwörter
Kostenanalyse · Docetaxel · Ressourcen · Mammakarzinom · Adjuvante Chemotherapie

Zusammenfassung
Hintergrund: Die Standardtherapie des nodal-positiven primären Mammakarzinoms bilden heute Taxan-haltige Regime. In aktuellen Studien konnten jedoch größere Patientensubgruppen identifiziert werden, die möglicherweise von dieser Therapie nicht profitieren. Um die mit der Einführung Taxan-basierter Chemotherapien verbundene Steigerung des Ressourcenverbrauchs und der Kosten abschätzen zu können, verglichen wir ein modernes sequentielles Regime (4× Epirubicin/Cyclophosphamid; 4× Docetaxel: EC→DOC) mit der kostengünstigen CMF-Therapie. **Patienten und Methoden:** Die Datenerhebung erfolgte parallel zur Phase-III-WSG-AGO-Intergroup-Studie (2000–2005). Eine Kohorte von 110 Patientinnen mit 1047 Chemotherapiezyklen an 38 Studienzentren wurde aus der Perspektive des Krankenhauses analysiert. **Ergebnisse:** Das durchschnittliche Alter betrug 52,4 Jahre. Die durchschnittlichen Kosten für eine EC→DOC Therapie (n = 54) beliefen sich auf € 8459 pro Patientin (95% confidence interval (CI): € 7785–9132). Hiervon verursachten die reinen Zytostatikakosten den größten Anteil. CMF war im Vergleich signifikant (–41,2%) kostengünstiger (€ 4973; 95% CI: € 4706–5240). Gleichzeitig konnte im CMF-Kollektiv die Anzahl toxizitätsassoziierter Krankenhausaufenthalte halbiert werden (CMF: n = 4, EC→DOC: n = 8). **Schlussfolgerungen:** Unsere Ergebnisse beschreiben eine substantielle Kostensteigerung, die die Einführung von sequentiellem Docetaxel in die adjuvante Chemotherapie des Mammakarzinoms nach sich zieht. Die vorgestellten Daten können zukünftig zur Ermittlung der Kosteneffektivität individualisierter Chemotherapiestrategien herangezogen werden.

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Introduction

Since the publication of Bonadonna's and Fisher's trial results over 30 years ago [1, 2], adjuvant chemotherapy has become essential in the management of early breast cancer. Six cycles of a polychemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) became the gold standard for decades with an overall reduction in the relative risk of relapse of 29% and of death from all causes of 21% after a 30-year follow-up [3].

The introduction of new drugs including anthracyclines [4–6] and taxanes [7–9] has improved outcome compared to the CMF regimen. In node-positive patients, a taxane-containing regimen is therefore considered the current standard therapy. However, these significant advantages in efficacy attributable to taxane-containing regimens were rather small. Considering all available phase III trials, taxane-based adjuvant chemotherapy for early breast cancer added absolute benefits in disease-free survival (DFS) and overall survival (OS) in favor of taxanes ranging from 3.3 to 4.6% and from 2.0 to 2.8%, respectively [10]. Moreover, these new drugs were associated with greater acute and long-term toxicity [11–13] as well as substantially higher drug acquisition costs in comparison to CMF [14]. With the current pressure on health care budgets, calculation of cost implications using new drugs in the adjuvant setting is mandatory. This is especially true in the light of recent evidence that anthracycline- or taxane-containing schedules might not be appropriate for distinct patient subgroups, such as the majority of premenopausal patients with HER2-negative, node-positive breast cancer [15, 16] or patients with HER2-negative and endocrine-responsive disease [17–19]. For some of these patients, CMF or even no cytotoxic but rather endocrine therapy alone may be adequate.

In 2000, the German WSG-AGO Intergroup started a prospective, randomized, multicenter phase III trial (EC→DOC) comparing the efficacy of an adjuvant taxane-containing chemotherapy (4 cycles of epirubicin and cyclophosphamide followed by 4 cycles of docetaxel) to a standard regimen in primary breast cancer patients with 1–3 positive axillary lymph nodes. According to the St. Gallen Consensus recommendations at that time, the standard regimen was CMF polychemotherapy [20–23]. In 2001, the results of a meta-analysis (published as full paper in 2005 [24]) were presented at the St. Gallen Conference and reported significant absolute advantages of 3.5% for DFS and 4.6% for OS in favor of anthracycline-containing regimens such as FEC (fluorouracil, epirubicin, cyclophosphamide) compared to CMF. Based on these data, participating EC→DOC study centers were allowed to choose between CMF and FEC (500/100/500 mg/m^2) for their control group. Consequently, the history of the EC→DOC trial reflects the continuous development of systemic treatment for breast cancer during the last decade and provides an ideal opportunity to assess the associated increase in costs.

In this study, we compared the modern sequential anthracycline- and taxane-containing chemotherapy regimen EC→DOC with the old standard CMF regimen regarding costs of health resource consumption. Data from 110 consecutive patients treated in 38 study centers were obtained from the EC→DOC trial data base.

Patients and Methods

Study Design

This prospective, longitudinal, randomized multicenter incremental cost analysis was conducted from 4/2000 to 5/2002. Patient data were retrieved from the Phase III WSG-AGO Intergroup EC→DOC trial which was open for recruitment from 04/2000 until 8/2005. Eligible for this trial were patients with histologically confirmed primary, node-positive breast cancer with 1–3 positive axillary lymph nodes treated by standard surgery (breast-conserving therapy (BCT) in combination with axillary lymph node dissection or modified radical mastectomy (MRM). Patients were randomized to either a standard of 6 cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 i.v. day 1 + 8 every 4 weeks) or the experimental taxane-containing 'EC→DOC' regimen consisting of 4 cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 i.v. day 1, every 3 weeks) followed by 4 cycles of docetaxel 100 mg/m^2 i.v. day 1, every 3 weeks. After 2001, a standard of 6 cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 i.v. day 1, every 3 weeks) was allowed alternatively to CMF. To attain 2 homogenous patient cohorts for the current cost analysis, only patients with completed CMF or EC→DOC chemotherapy and locked data monitoring – included in the EC→DOC trial data base until first toxicity analysis in 5/2002 – were eligible.

Perspective

The analysis was conducted from the hospital provider's perspective.

Resource Utilization and Costs

Resource utilization data were collected prospectively from initiation to termination of adjuvant chemotherapy or during rehospitalization due to toxicity. Data examples measured during chemotherapy application included: mean dose of chemotherapeutics; application mode of epirubicin; hospital services for chemotherapy application; length of inpatient stay; frequency of supportive drugs. Data examples measured during rehospitalization due to therapy-associated toxicity included: number of rehospitalizations; number of patients rehospitalized; mean duration of rehospitalization; resource use during hospitalizations; frequency and number or treatment days; resource use during hospitalizations (platelet and red blood transfusions, use of chest X-rays or other diagnostic procedures; colony stimulation factors (CSFs); antibiotics, fungistatics; other drugs; non-medical treatments (e.g. acupuncture, consultations).

Diagnostic Effort Associated with Chemotherapy Application

Diagnostic efforts associated with chemotherapy application, including the week before the first chemotherapy visit and 3 weeks after the last chemotherapy visit, were estimated by a comprehensive retrospective chart review in one participating study center (n = 8 patients who had completed their adjuvant chemotherapy). Resource use caused by initial staging and primary surgery was excluded.

Medical Devices for Chemotherapy Application

Number of medical devices used during 1 chemotherapy cycle day was analyzed and reported by the responsible study nurse of one participating study center (Klinikum rechts der Isar der TUM, Dept. of Gynecology: e.g. all infusion-related materials including infusion system, connection devices, i.v. puncture devices, blood storage containers such as EDTA monovettes, etc.).

Table 1. Sources of unit costs

Resources	Unit costs	Sources of unit costs
Drugs, infusions, blood products, infusion bags	€ per unit	local costs of the TUM, Nov. 2005
Pharmacy and transport services	€53 and €1.9 per preparation	Hilfstaxe (contractual unit costs of retail pharmacist services), Jan. 2006; hospital administration of the TUM, Nov. 2005
Medical devices	€ 7.9 per chemo cycle day	local costs of the TUM, Dept. of Gynecology, Nov 2005
Diagnostic efforts	€ 41 (CMF) € 38 (EC→DOC) per chemo cycle day	blood and serum diagnostic: local costs of the TUM, Dec. 2005; diagnostic tests: standard rate of the German Hospital Federation (DKG-NT) 2002, column 7: full cost
Staff time drug administration[a]	€ 99 per chemotherapy cycle day	internal statistics of the TUM, Dept. of Gynecology, Jan. 2005; Bavarian Ministry of Finance: average personnel cost since 2004
Basic hospital costs	€ 29 (outpatient, day care) € 59 (inpatient) per chemo cycle day	Federal Statistical Office, subject series 12, volume 6.3: hospital costs 2001 per day[b]
Hospital costs per day	€ 325	Federal Statistical Office, subject series 12, volume 6.3: hospital costs 2001 per day[c]
Port implantation (subclavian vein)	€377	modeled on the DKG-NT 2002, column 7: full cost
Insertion of a central venous catheter	€95	modeled on the DKG-NT 2002, column 7: full cost

[a]Including organization, documentation, billing.
[b]Adjusted by 5.25% annually to convert 2001 basic hospital costs to 2005.
[c]Used as an estimate of basic hospital and personnel cost per day of rehospitalization. Costs of medical and diagnostic procedures shown in table 5 were added on top.

Calculation of Staff Time per Chemotherapy Cycle Day

Based on the knowledge of the number of chemotherapy cycle days, staff structure, and staff time per year attributable to organization, administration, documentation, and billing of adjuvant breast cancer chemotherapy, we were able to calculate staff time per chemotherapy cycle day. All necessary data were derived from internal statistics of the hospital pharmacy and clinic management of the Dept. of Gynecology (Klinikum rechts der Isar der TUM) and are not routinely available. The working time required was multiplied by the average hourly salaries and benefits for each group of professionals separately and then added together.

Rehospitalization Costs

For calculation of rehospitalization costs attributable to toxicity, the duration of the stay was multiplied with a mean estimate of German hospitalization costs per day. Costs of transfusions, drugs, diagnostic procedures, and non-medical treatment were added. Results were reported as rehospitalization costs per patient treated with EC→DOC or CMF adjuvant chemotherapy.

Other Costs

Other costs of resources were determined using German unit cost from the hospital provider's perspective. Unit costs and sources of unit costs are shown in table 1. Estimates of costs were reported as the quantity of different resources consumed. The overall chemotherapy-related costs per patient (mean) were evaluated separately for each treatment arm. The incremental costs (cost difference between EC→DOC and CMF) described the additional costs attributable to sequential docetaxel in primary chemotherapy of breast cancer. Due to the short observation period, we report in undiscounted November 2005 EUROs.

Sensitivity Analysis

To account for uncertainties caused by applying German cost data to healthcare resource utilization data observed in the EC→DOC trial, one-way sensitivity analysis was performed for docetaxel acquisition costs (85 and 115% of base case value) and basic hospital costs (0% of base case value). Proportions of patients with an early treatment stop may differ if analyzed in a larger study population. Therefore a subgroup-based sensitivity analysis was conducted to consider relevant differences in costs attributable to sequential docetaxel for patients with completed adjuvant chemotherapy in comparison to patients with a premature treatment stop, e.g. because of side effects.

Table 2. Patient characteristics at baseline

Characteristics	EC→DOC mean (95% CI)	CMF mean (95% CI)
Patients for cost analysis, n	54	56
Age[a], years	51 (49–54)	53 (51–56)
Height, cm	164 (163–166)	163 (159–167)
Weight, kg	69 (66–72)	72 (67–76)
Body surface, m^2	1.75 (1.71–1.79)	1.75 (1.71–1.79)
Tumor size, cm	2.3 (2.0–2.6)	2.2 (1.9–2.4)
Grading, G1–3	2.4 (2.3–2.5)	2.3 (2.1–2.4)
Premenopausal status, %	52 (39–65)	57 (44–71)
No comorbidities, %	65 (52–78)	50 (37–63)

[a]Age at first chemotherapy application.

Statistics

Distribution of resource utilization was described as frequency or number of utilized services per patient, separated by type of service and treatment arm. Descriptive statistics (mean, median, minimum, maximum, standard deviation, and 95% confidence intervals (CI)) were performed for costs and other continuous variables. Categorical variables were given with relative frequencies and 95% CIs respectively. The t-test for two independent samples or chi-square test was used for explorative two-group comparisons. Any p values given are two-sided. The SAS system 8.0 (SAS Institute Inc., Cary, NC, USA) or Microsoft Excel™ (2002) was used for tabulations and statistical evaluation.

Table 3. Chemotherapy and hospital services for chemotherapy application

Parameter	EC→DOC (n = 54)[a] mean (95% CI)	CMF (n = 56)[a] mean (95% CI)
Mean cycle number per patient, n	7.4[b] (7.1–7.8)	5.8 (5.6–6.0)
Number of chemotherapy cycle days, n	400	647[c]
Patients not completing all cycles of therapy		
n	12	4
%	22[b] (11–33)	7 (0–14)
Mean cycle number, n	5.3[b] (4.4–6.3)	3.3 (2.8–3.7)
Reasons for incomplete chemotherapy, n		
Toxicity	9	2
Tumor progression	–	1
Other reasons	3	1
Mean dose of chemotherapeutics[d], mg		
Methotrexate	–	73 (70–46)
5-Fluorouracil	–	1,054 (1,047–1,062)
Cyclophosphamide	1,046 (1,035–1,058)	1,047 (1,039–1,054)
Carboplatin[e]	–	540
Epirubicine	157 (155–158)	–
Docetaxel	173 (170–173)	–
Epirubicin applications, n	213	–
Application mode epirubicine, %		
Peripheral	80 (75–80)	–
Port	16 (11–21)	–
Central venous catheter	4 (2–7)	–
Hospital services for chemotherapy application, %		
Outpatient	58 (54–62)	61 (56–66)
Day care[f]	17 (14–20)	17 (13–20)
Inpatient	25 (21–28)	23 (19–27)
Mean length of inpatient stay, days %	2.7 (2.4–3.1)	2.5 (2.3–2.7)

[a]Patients available for cost analysis; missing data were excluded from analysis.
[b]p value < 0.05 from t-test on independent samples or chi-square test.
[c]1 cycle of CMF contains 2 chemotherapy cycle days (days 1 + 8).
[d]Absolute amount per chemotherapy cycle day.
[e]1 accidental carboplatin application.
[f]Individual flat rate for 24 h inpatient stay.

Results

Patient Baseline Characteristics

A cohort of 110 consecutive patients (EC→DOC n = 54; CMF n = 56) receiving 1,047 chemotherapy cycle days at 38 study centers (university hospitals n = 12; others n = 26) was identified based on the chosen selection criteria. Mean patient age was 52.4 years (standard deviation 9.0). Baseline characteristics of the two treatment arms compared in this incremental cost analysis are listed in table 2. Although the portion of patients without comorbidities was somewhat lower in the EC→DOC group, no statistically significant differences in baseline characteristics were detected.

Chemotherapy and Hospital Services for Chemotherapy Application

In total, patients received chemotherapy on n = 400 chemotherapy cycle days in the EC→DOC group compared to n = 647 in the CMF group, with a higher cycle number per patient in the EC→DOC group (7.4 vs. 5.8). The EC→DOC arm contained more patients with incomplete chemotherapy (n = 12) mainly due to toxicity (n = 9). Treatment interruption occurred on average after the first docetaxel-containing cycle. Table 3 summarizes the mean doses of chemotherapeutics per chemotherapy cycle day and treatment group. The mode of epirubicin application was mainly peripheral i.v. (80%). A port system was used in 16% and a central venous catheter in 4% of applications. There was 1 accidental carboplatin infusion in the CMF arm. The majority of patients (59%) received chemotherapy mainly in an outpatient setting, while 17% visited a day care unit, and 24% were hospitalized for about 2.5 days. There was no difference in the distribution of hospital services for chemotherapy application between treatment groups.

Supportive Therapy

Frequency of supportive drug use during hospital stay for chemotherapy application is reported per treatment group and chemotherapy cycle day (table 4). In the EC→DOC

Table 4. Frequency of supportive drug use during hospital stay for chemotherapy application

	EC→DOC mean (95% CI)	CMF mean (95% CI)
Chemotherapy cycle days with supportive drug use, n	384[a]	632[a]
5-HT3 receptor antagonists, %	83[b] (77–87)	95 (93–97)
Corticosteroids, %	86[b] (83–90)	69 (66–73)
D2 receptor antagonists, %	20[b] (16–24)	27 (24–31)
Antidepressants, %	2.1 (0.9–4.1)	1.3 (0.6–2.5)
H1 receptor antagonists, %	15[b] (11–19)	2.2 (1.2–3.7)
H2 rezeptor antagonists, %	13[b] (10–17)	0
Mesna, %	54[b] (49–59)	88 (86–91)
Antacids, proton pump inhibitors, %	0.3 (0–1.4)	1.0 (0.4–2.1)
Low molecular heparins, %	1.3[b] (0.4–3.0)	0

[a]Chemotherapy cycle days available for analysis of supportive drug use; missing data were excluded from analysis, thus, in percent calculations the denominator may vary somewhat.
[b]Two group comparison yields two-sided p value < 0.05 from t-test for independent samples or chi-square test.

Table 5. Toxicity associated rehospitalizations

Parameter	EC→DOC (n = 53)[a]	CMF (n = 55)[a]
Number of rehospitalizations[b], n	8 times in 7 patients	4 times in 4 patients
Patients rehospitalized, % (95% CI)	13 (4–22)	7 (0–14)
Mean length of rehospitalization, days (95% CI)	5.9 (2.4–9.4)	6.3 (4.4–8.1)
Resource use during hospitalizations		
Use of platelet transfusions, %[c] (n[d])	0 (0)	0 (0)
Use of red blood cell transfusions, %[c] (n[d])	12.5 (1)	0 (0)
Use of chest X-rays, %[c] (n[d])	50 (1)	0 (0)
Other diagnostic effort e.g. ultrasound, %[c] (n[d])	25 (2.5)	25 (1)
Use of G-CSF, days	37.5 (1.3)	100 (4.3)
Treatment with antibiotics, fungistatics, days	75 (4.8)	50 (4.5)
Treatment with other drugs, days	75 (2.3)	75 (1.6)
Non medical treatment e.g. acupuncture, %[c] (n[d])	12.5 (2)	0 (0)
Consultations, %[c] (n[d])	12.5 (1)	0 (0)
Mean cost per rehospitalization, € (95% CI)	2,070 (922–3,218)	2,488 (2,069–2,906)

[a]Missing data for 1 patient per treatment group.
[b]Not for primary surgery or chemotherapy.
[c]% of rehospitalizations.
[d]Mean number of units consumed or treatment days (if stated separately) during rehospitalizations with resource use.
G-CSF = Granulocyte colony-stimulating factor.

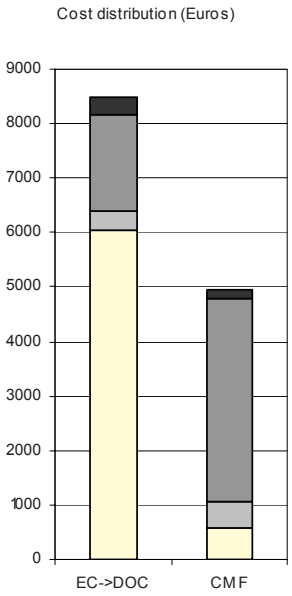
group, less 5-HT_3 and/or D_2 receptor antagonists but more corticosteroids were used. The nephroprotective drug Mesna was given in 54% of EC→DOC cycles. H_1 and/or H_2 receptor antagonists were used in 15 and 13% of EC→DOC cycles, respectively. Drugs with a low application frequency were antidepressants, gastroprotective agents, and low molecular heparins.

Rehospitalization due to Toxicity

Seven patients receiving EC→DOC were rehospitalized due to toxicity for a combined total of 8 times. Although not statistically significant, the percentage of EC→DOC patients who needed rehospitalization was almost twice that of the CMF group (13 vs. 7%). The average duration of rehospitalization was 6 days in both treatment arms. Mean number of units consumed per rehospitalization together with the respective resource use are summarized in table 5. Antibiotics and/or fungistatics were given for 4.8 days in 75% and granuloctye colony-stimulating factor (G-CSF) support in 38% of the patients rehospitalized because of EC→DOC-related side effects. No platelets and only 1 unit of red blood cells were transfused. Overall costs per rehospitalization were similar in both arms with €2,070 in the EC→DOC vs. €2,488 in the CMF group, respectively.

Costs, Cost Analysis

Chemotherapy related costs according to treatment arm and incremental costs for sequential docetaxel are detailed in figure 1. Mean direct costs for the EC→DOC group totaled €8,459 per patient (95% CI: €7,785–€9,132). Costs for cyto-



Costs per patient	EC→DOC mean €	(%)	CMF mean €	Δ Costs mean €
Total base case	*8,459**	*(100)*	*4,973*	*+3,486*
Cytostatic drugs	5,673*	(67)	75	+5,598
Supportive drugs	267	(3.2)	355	–88
Medical devices, infusion bags	87*	(1)	156	–69
Diagnostic efforts	283*	(3.3)	469	–186
Port or catheter implantation	93*	(1.1)	0	+93
Staff time drug administration	734*	(8.7)	1,137	–403
Pharmacy services including transport	623*	(7.4)	1,887	–1,264
Basic hospital services[a]	414*	(4.9)	705	–291
Toxicity-associated rehospitalization	313	(3.7)	181	+132

Fig. 1. Chemotherapy-related costs by treatment and incremental costs for sequential docetaxel (hospital provider's perspective).
[a]Fixed rate for e.g. accommodation and catering.
*Two-group comparison yields two-sided p-value < 0.05 from t-test for independent samples.

Table 6. One way sensitivity analysis

	% of base case value	Costs per patient, mean (95% CI), € EC→DOC	CMF	Δ Costs
Base case		8,459 (7,785–9,132)	4,973 (4,706–5,240)	+3,486
Docetaxel acquisition costs	115	9,256 (8,513–9,998)	4,973 (4,706–5,240)	+4,283
Docetaxel acquisition costs	85	7,662 (7,055–8,269)	4,973 (4,706–5,240)	+2,689
Basic hospital costs	0	8,034 (7,391–8,678)	4,255 (4,083–4,426)	+3,779

Table 7. Subgroup-based sensitivity analyses

	Costs per patient, mean (95% CI), € EC→DOC	CMF	Δ Costs
Base case	8,459 (7,785–9,132)	4,973 (4,706–5,240)	+ 3,486
Patients with complete chemotherapy	9,381 (8,983–9,779)	5,051 (4,785–5,316)	+ 4,330
Patients with premature treatment stop	5,461 (3,763–7,159)	4,002 (2,880–5,125)	+ 1,459

statics accounted for the largest portion with €5,673 (67%), whereas staff costs for drug application and pharmacy services including transport averaged at €1,357 (16%); average basic hospital costs were €414 (4.9%) with an additional €376 (4.4%) attributable to diagnostic efforts and port or catheter implantation. Hospitals spent €354 (4.2%) on supportive drugs, i.v. administration devices, and infusion bags. Rehospitalization due to chemotherapy toxicity accounted for €313 (3.7%).

In contrast, CMF was significantly €3,486 less expensive (–41.2%) with mean costs of €4,973 (95% CI: €4,706–€5,240). Savings for CMF acquisition with –€5,598 were partially compensated by higher costs for medical and diagnostic efforts or pharmacy and hospital basic services due to the day 1 and 8 application schedule (total of 12 application days) in contrast to EC→DOC with a day 1 only schedule (total of 8 application days).

Sensitivity Analysis

Referring to sensitivity analysis, results were most sensitive regarding docetaxel acquisition costs, whereas exclusion of basic hospital costs only slightly impacted on EC→DOC-associated incremental costs. The range was €2689–€4,283 (table 6). Subgroup-based sensitivity analysis showed 66.3% lower incremental costs for patients with a premature treatment stop compared to patients who completed their adjuvant chemotherapy (€1,459 vs. €4,330; table 7).

Discussion

The introduction of new drugs and rapidly changing algorithms for selecting patients has significantly changed the landscape for adjuvant breast cancer therapy [25]. In contrast, the evaluation of the economic consequences is well behind,

although pressures on health care budgets are constantly rising. In the light of diagnosis-related groups (DRG) or flat rate-based reimbursement, especially hospital health care providers or hospital-associated medical institutions are forced to improve treatment cost transparency and optimize resource allocation. With the aim of providing economic data to enable optimization of hospital-based chemotherapy management, we therefore performed this prospective incremental cost analysis selecting sequential docetaxel as an example for an innovative but expensive chemotherapy regimen. CMF was chosen as comparator because it has been the gold standard for decades and still may be appropriate for distinct patient subgroups at low toxicity and cost [17, 25, 26].

Data of resource consumption was mainly collected prospectively alongside the German phase III WSG-AGO Intergroup EC→DOC trial for a cohort of 110 patients receiving over one thousand chemotherapy cycle days in 38 study centers. Cycle number differed between the chemotherapy regimens compared (6 cycles of CMF day 1 and 8 every 4 weeks vs. 4 cycles EC followed by 4 cycles of docetaxel day 1, every 3 weeks), hence treatment costs are exclusively comparable on a per patient level. The appropriate patient cohort was therefore selected taking into account completeness of adjuvant chemotherapy out of those 395 patients randomized at the time of the first EC→DOC toxicity analysis in 5/2002.

To date, this is the first prospective incremental cost analysis comparing a modern taxane-containing adjuvant regimen to an older standard regimen with lower toxicity and cost. Although performed from a German hospital provider's perspective, incremental cost estimates from this study seem to be transferable or easily adjustable to other health systems and imply identical or similar conclusions and results. As is common for innovative chemotherapy, the main cost factor are the cytostatic drugs themselves, accounting for 67% of EC→DOC-related total costs. In contrast, 75% of CMF-associated costs are caused by hospital pharmacy, medical, and basic services. They partially compensate the high drug acquisition costs for sequential docetaxel (€5,673) and therefore reduce incremental costs to +€3,486 with a consequential 70% budget increase. Due to lack of microeconomic data, cost management of oncologic therapies in the past was often performed exclusively based on drug acquisition costs [14]. In reference to our results, underestimation of true costs and overestimation of incremental costs of the innovative therapies is the consequence. Moreover, the presented data will facilitate hospitals to optimize financial management of clinical trials [27].

Hospitals continuously adapt services for chemotherapy application based on reimbursement. Nowadays, chemotherapy is mainly administered in outpatient facilities with a lean staffing level. Thus, current costs for pharmacy and medical service might be lower with an inverse effect on EC→DOC-associated incremental costs. In contrast, basic hospital costs – which double for inpatient treatment (inpatient: €59; outpatient/day care €29) – did not have any relevant influence in our analysis. Docetaxel acquisition costs and the percentage of patients with incomplete chemotherapy were identified as variables with a high impact on incremental costs. Our results demonstrate a threefold higher drop-out rate for EC→DOC in comparison to CMF (22 vs. 7%, respectively). Although a drop-out rate of 24% was already reported for adjuvant sequential dose-intense paclitaxel [8], our high drop-out rate could also be attributable to a selection bias. Proportions of patients with an early treatment stop may thus differ if analyzed in the total study population of the EC→DOC clinical trial.

Clinical Implications and Future Health Economic Research

In health economic evaluation of adjuvant breast cancer chemotherapy, cost data have to be evaluated in connection with health outcomes to ascertain the most efficient therapy option. As the number of treatment strategies and new targeted therapies such as biologicals or small molecules [28–31] is constantly rising, cost-effectiveness or cost-utility will become an increasingly important endpoint of future trials [32].

In 2005, the Oxford Overview concluded that further improvements in long-term survival could be achieved by implementation of new drugs but also by better use of established drugs [24]. Better use in this context could mean identifying the optimal drug for the individual patient. Traditionally, the decision for administering adjuvant chemotherapy in early breast cancer patients has been based on the risk of relapse. Modern therapy strategies, however, attempt to treat the target rather than to treat the risk. Therefore, it will be crucial to define predictive markers in order to target the optimal treatment to the individual patient. In this context, several markers already seem to be close to the clinic: Topoisomerase IIα amplification may play a decisive role in predicting chemosensitivity of breast cancers to anthracyclines [33–37]. Beta-tubulin isotypes in breast cancer cells seem to be a promising predictive marker of docetaxel activity [38, 39]. Recent data suggest, that HER2-negative, node-positive patients with hormone receptor-positive tumors may not profit from taxane and in particular from paclitaxel therapy [18]. Moreover, BRCA1 dysfunction may play a role in the pathogenesis of sporadic basal-like cancers [40, 41]. Through repair of double-stranded DNA breaks, the BRCA1 gene product helps to maintain genomic integrity due to its participation in the cellular response to DNA damage. To utilize this disability to recover from DNA damage, platinum-containing agents or alkylating agents like cyclophosphamide that cause DNA destruction may be the right choice for treating such basal-like breast cancers. Last but not least, recent studies suggest that gene expression assays can help to distinguish breast cancers patients at low or high risk for relapse and breast cancer-related mortality [42–44].

In summary, for a substantial number of breast cancer pa-

tients, a cost-saving and less toxic chemotherapy like CMF, followed by an endocrine therapy or even no cytotoxic therapy at all may be as effective as more modern anthracycline- or taxane-containing regimens. More precise treatment stratification could therefore avoid overtreatment, side effects, and reduce medical expenditures for patient subgroups that will not benefit from adjuvant chemotherapy at all or certain drugs in particular. The results of this analysis reflect the striking increase of costs within only 1 decade caused by introduction of new chemotherapeutic agents and will support hospitals to optimize financial management of chemotherapy. Furthermore, the results of this study may be used to analyze cost-effectiveness of individualized adjuvant breast chemotherapy strategies for which CMF or CMF-like schedules are still an adequate therapeutic option.

Conflict of Interest

Nadia Harbeck: honoraria (Sanofi-Aventis), consulting (Sanofi-Aventis); Ulrike Nitz: honoraria (Sanofi-Aventis, Amgen);
Angela Ihbe-Heffinger: research grant (Sanofi-Aventis). The other authors do not have any conflicts of interests.

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