Adjuvant Cyclophosphamide, Methotrexate, Fluorouracil (CMF) in Breast Cancer

Is it Cost-effective?

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Adjuvant chemotherapy (ACT) may expose patients to morbidity, with little gain in outcome. Treatment with CMF (cyclophosphamide, methotrexate, fluorouracil) has been the standard ACT in several countries for decades. In this model, efficacy, tolerability and quality of life data from the English-language literature were incorporated with Norwegian standard ACT practice and cost data in a cost-effectiveness/cost-utility approach. The CMF efficacy was calculated as 2.45 years saved per patient treated. The quality of life was assumed diminished by 0.33 (0–1 scale) for 6 months and the life years gained were valued Q = 0.86. An 85% dose intensity was employed, one British pound (£1) was calculated as 12 NOK and a 5% discount rate was used. The total cost of adjuvant CMF, including amounts spent on drugs, administration, travelling and production loss, was calculated to £2365–£6253, depending on the method chosen. Money spent on drugs alone constituted 13–34%. The cost per life year saved was measured as £2170–£5737. A cost-utility approach revealed a cost per quality-adjusted life year (QALY) of £2973–£7860. Adjuvant CMF in breast cancer is cost-effective in Norway.

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Breast cancer is a significant healthcare problem world-wide and is the most common form of cancer among women in North America and throughout Europe (1–4). More than half a million women develop breast cancer every year, leading to the estimate that the disease will affect at least 5 million women world-wide in the next decade (3, 5). Adjuvant chemotherapy offers delayed time to recurrence and prolonged survival (6) but the incidence of breast cancer is still increasing by about 1–2% per year (1). However, the great majority of this increased incidence is observed in stage I disease (7). Thus, despite the altered incidence, the age-adjusted mortality rates for breast cancer have remained almost stable for the past 50 years (8). The prognosis of breast cancer depends upon its stage. The survival figures in Norway in stages I and IV are 88.3% and 14.5%, respectively (7). Several prognostic indicators are useful in selecting patients who are the most likely to benefit from adjuvant therapy. The most important predictors for survival in invasive breast cancer are tumour size, the presence or absence of axillary node metastasis and histological features, such as tumour grade. Proliferation markers such as ploidy, S-phase and new biological markers such as c-erb-B2, bcl-2 and p-53 are indicators of disease aggressiveness. However, although useful, they have relatively limited availability and the individual contribution of some of these markers to patient outcome still requires validation.

Recently, an international consensus panel on the treatment of primary breast cancer recommended that only the minority of patients, with an at least 90% survival probability to 10 years, should not receive adjuvant systemic therapy routinely (1). In Norway, the Norwegian Breast Cancer Group (NBCG) has recommended adjuvant chemotherapy consisting of cyclophosphamide, 5-fluorouracil and methotrexate (CMF) for 6 months (9 cycles) in some stage I (T2 tumours with histological grade II–III) and all stage II patients under 55 years of age (oestrogen receptor-negative patients less than 65 years).

The high incidence of breast cancer and the treatment costs indicate that the diagnosis and treatment of this malignancy place a significant financial burden on the healthcare system. Today, the CMF regimen has been the 'gold standard' in adjuvant chemotherapy for more than a decade. In Norway, we have good quality data on costs. In the future, anthracyclin-containing regimens (e.g. FEC–fluorouracil, epirubicin, cyclophosphamide) may replace

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CMF. Cost-effectiveness analysis will be one of the important factors in the decision between these two regimens. This study was undertaken to evaluate the cost-effectiveness of adjuvant CMF therapy in Norway using a model based on the available national cost data and studies from the international English-language literature documenting the efficacy of this regimen.

MATERIAL AND METHODS

In a cost-effectiveness analysis, we have to include data on efficacy as well as costs. In this study, data from the literature on efficacy of adjuvant CMF chemotherapy, tolerability, quality of life, drug charges and production gains/losses were included. All articles on adjuvant chemotherapy in breast cancer registered in the Medline database from 1986 to 1998 were selected for investigation, making a total of 778 articles citing the words 'breast cancer' and 'adjuvant chemotherapy'. Subgroups of articles were selected in order to find articles containing the words 'quality of life', 'cost' and 'CMF'. These data were examined to clarify the efficacy and quality of life (QoL) associated with CMF. A summary is presented in Table 1.

Efficacy of adjuvant CMF

In the earliest years of adjuvant chemotherapy in breast cancer, single chemotherapeutic drugs such as melphalan were used (9). The first large-scale trial of CMF was carried out between 1973 and 1975 (10). This trial, conducted in Milan, investigated the use of 12 cycles of CMF versus no treatment in pre- and postmenopausal women with lymph-node-positive breast cancer. There was a highly significant difference favouring the CMF regimen versus the control in disease-free survival (109 months) in premenopausal women. However, in postmenopausal women, the benefit was only 5 months. Many similar studies included in the first overview of all the available randomized studies that were published in 1990 showed a consistent trend. In 1992, a second overview was published from the Early Breast Cancer Trialists' Collaborative Groups (EBCTCG) (11). ACT prolonged disease-free and overall survival in both pre- and postmenopausal women. The relative risk of recurrence was reduced by up to 30%. However, the effect was low in postmenopausal women. Today, 6 months' ACT with combination chemotherapy confers all the advantages that have been associated with longer use (11–13). At present, we have 20 years' follow-up data on CMF (14). The optimal length of treatment with ACT still remains to be established. However, an International Breast Cancer Study Group trial (n = 1554) revealed six cycles of CMF to be superior to three cycles (15). In 1998, at the 6th International Conference on Adjuvant Therapy of Primary Breast Cancer, in St. Gall, Switzerland, two reports (16, 17) including a total of 463 CMF-treated patients reported that, with adjuvant CMF for 6 months, a 5-year overall survival of 70 and 71%, respectively, had been achieved. Recently, a new overview of 69 randomized polychemotherapy trials involving about 30000 women with early breast cancer was performed by the EBCTCG (18). Most of these studies included the CMF regimen. The improvement in 10-year survival was between 7 and 11% in premenopausal women, depending on nodal status (7% (71–78%) in node-negative and 11% (42–53%) in node-positive). The figures in node-positive and node-negative women aged 50–69 years were 3% (46–49%) and 2% (67–69%), respectively. All these randomized studies confirm the 8.5% improvement in 10 years' survival documented by the Milan study (19).

In an economic analysis the effectiveness is described as the number of life years gained during the expected lifespan of an individual. During the first 10 years, the difference between the control and the CMF group in the Milan study was 51 years/100 patients (19, 20) and the 10-year survival figures were 48% and 56.5%, respectively. Data from the NBCG (7) indicate a median age of 50 years among breast cancer patients receiving adjuvant chemotherapy in Norway. Calculating a median age of 50 years, an 8.5% (56.5–48%) difference in survival 10 years later and the life expectancy of Norwegian women aged 60 of 22.8 years (Statistics Norway), the Norwegian figures indicate 2.45 life years gained (0.51 years + 22.8 years∗0.085) per patient treated. This estimate is in accordance with the 2.4 life years calculated by Irvin & Kuhn (21). Gains occurring in the future have to be discounted. Employing a 5% discount rate according to the recommendations of Luce & Elixhauser (22) and calculating the 10-years' benefit equally distributed (10% per year), the discounted figure is 1.09 life years (LY) (0.39 years + 8.24∗0.085). This finding is strongly supported by the estimated overall survival of 862 and 756 discounted years per 100 node-positive breast cancer patients (862–756/100 = 1.06 LY) reported by Trippoli et al. (23).

Table 1

Efficacy and quality of life data implemented in a model for cost-effectiveness and cost-utility analysis in adjuvant CMF therapy in breast cancer

Efficacy
—Median age at initiation of CMF of 50 years
—51 years gained per 100 women treated during the first 10 years
—An improved 10-year survival of 8.5% following adjuvant CMF
—Expected life years of 10 years survivors calculated 22.8 years
Quality of life
—Quality of life decreased by 0.33 (0–1 scale) for 6 months during therapy
—A quality of life of 0.86 following adjuvant CMF lasting for the rest of life

Adjuvant CMF and quality of life (QoL)

Adjuvant CMF is associated with several side effects. Hair loss, myelosuppression, anorexia, nausea, vomiting, mucositis, leucopenia and amenorrhoea are among the acute adverse events. However, especially nausea and vomiting can be significantly suppressed by the use of steroids and new antiemetic drugs. Quality of life in CMF therapy was addressed by Gelber et al. (24) in a meta-analysis of nine trials (n = 3920). Within 7 years of follow-up, it was found that ACT did not increase QoL survival time to any greater extent than treatment with tamoxifen alone. According to Rensing and associates (25), QoL is reduced by the unpleasant side effects of CMF during the treatment period. They observed that by using the EORTC QLQ C-30, a decrease of 0.33 in QoL (0–1 scale) in general from cycle 1–3 to cycle 4–6 (Q = 0.86 to Q = 0.53); 101 questionnaires were filled in by 64 breast cancer patients. It is reasonable to believe that there was a slight recovery in QoL on completion of ACT. Based on the information from the QoL studies in ACT, adjuvant CMF was calculated in this model as reducing QoL by 0.33 for 6 months and thereafter having no effect on QoL. The life years gained were evaluated as 0.86 on a 0–1 scale (25, 26). The reduction in QoL is supported by Ganz and co-workers (27), who did not find any significant difference in QoL in 1110 patients treated with breast-conserving surgery and tamoxifen, chemotherapy or no adjuvant therapy 1–5 years (median 2.8 years) following therapy. However, sexual functioning was significantly worse (more vaginal dryness and pain) in patients who had received any chemotherapy.

Direct healthcare costs

All costs were converted to British pounds at the rate of £1 = 12 NOK.

The drug costs of adjuvant chemotherapy were determined using the Norwegian price list, as of May 1998 (28, 29). The average body surface area calculated was (BSA) of 1.73 m^2. This was based on data from 5000 women with breast cancer (21). Expenses incurred through necessary antiemetic therapy were added. The standard regimen employed at our institution including ondansetrone 8 mg orally twice a day for 2 days and dexamethazone 20 mg i.v. once every course was implemented. The CMF version used in Norway is presented in Table 2. The chemotherapy administration costs in an outpatient setting were calculated according to the tariff of the National Health Administration (NHA) (29). Dose intensity will have a significant influence on chemotherapy costs but Irwin & Kuhn (21) did not account for this effect, while Løber et al. (30) reported a drug utilization amounting to only 59% of doses scheduled in the protocols. However, the figures of Løber and co-workers (30) were based on 12 months' adjuvant CMF therapy. Furthermore, their study was published back in 1988, a long time before the colony-stimulating factors (G-CSF) had been included in daily clinical practice. At the annual meeting of the American Society of Clinical Oncology (ASCO) in 1998, Hutchins et al. (31) reported a dose intensity of 90% in course 1–3 and 70% in course 4–6. These figures are supported by a dose intensity of 87% in 6 cycles of CMF in 104 patients reported by Galligioni and co-workers (32). Based on clinical experience and these data, a dose intensity of 85% was employed in this model.

Table 2

The table shows the CMF (cyclophosphamide, methotrexate, fluorouracil) version employed in adjuvant chemotherapy in breast cancer in Norway

Drug	Dose (mg/m^2)	Frequency	Total courses
Cyclophosphamide	600	Every 3rd week	9
Methotrexate	40	Every 3rd week	9
Fluorouracil	600	Every 3rd week	9

The drug administration costs at the pharmacy, University Hospital of Tromsø, were calculated according to the tariff of the National Health Administration (NHA) (£16.4/unit) (29). This amount constitutes the cost of drug preparation for intravenous administration. The women have to visit an outpatient clinic administrating the i.v. therapy. The tariff of public outpatient treatment valid from July 1st 1997 from the NHA was employed for the calculation of costs (29). The tariff for outpatient therapy covering hospital costs (doctors' and nurses' fees and laboratory tests) was £66.3 per visit.

In addition, amounts spent on travelling to undergo ACT have to be included. An average of £10 per trip employed in a Norwegian study on adjuvant chemotherapy was included in this model (33).

Indirect costs (non-health care costs)

In Norway, all employees have to pay an income-related tax to the National Insurance Administration (NIA). When reported ill by their doctors, the employees receive an income for up to one year, paid by the NIA. During adjuvant chemotherapy a significant number of women are reported ill and stay out of work because of the side effects of chemotherapy. No data on the number of women doing so could be obtained from the NIA. However, by questioning eight medical oncologists treating breast cancer patients at the University Hospital of Tromsø, a qualified guess of 35% staying out of work for a median period of 6 months during ACT was recommended. According to Statistics Norway, about half of the women in Norway aged 50 years are employed. For simplicity, it was assumed that we could take the mean cost of employment (Statistics Norway) including income, on-the-job training and social

expenses as a proxy for the value of it. The mean 1996 annual employment costs in Norway were £24667 per employee (Statistics Norway). There are for the moment two major recommendations on how to include indirect costs. The first is the friction cost method (34). This approach in effect implies that indirect costs are defined as the cost of replacing a sick worker. Essentially, Roijen et al. (35) divides the indirect costs into three components, namely absence from paid work, reduced productivity at paid work and unpaid production. Koopmanschap et al. suggest the cost to be 10% of the human capital (36). The other alternative is the human capital-cost approach (37). With this method the reduced future gross income resulting from mortality and/or morbidity is estimated. In the present model, both approaches were implemented.

RESULTS

The total cost of adjuvant CMF chemotherapy, including cost of drugs, administration, travelling and production loss, was calculated to £2365–£6253, depending on the method chosen. Details are presented in Table 3. The money spent on drugs alone constituted 13–34%. The major contributor to the cost is the drug administration or the indirect costs, depending on the approach selected.

A cost-effectiveness analysis revealed a cost per life year saved ranging from £965 to £2552. Employing the recommended 5% discount rate, the figures were £2170 (2365/(0.39 + (8.24∗0.085)) and £5737 (6253/(0.39 + (8.24∗0.085)), respectively. The discounting technique accounts for the fact that health benefits and pounds spent in the future are worth less than in the present.

By adding the quality of life dimension into the results of the cost-effectiveness analysis, a cost-utility approach can be indicated. With no discount rate, the cost per quality adjusted life year (QALY) was calculated to £1218 (£2365∗(0.86∗2.45–0.33∗1/2)) and £3220 (£6253∗(0.86∗2.45–0.33∗1/2)), respectively. Employing a 5% discount rate, the corresponding figures were £2973 (£2365/(0.86∗(1.09–0.33∗1/2)) and £7860 (£6253/(0.86∗(1.09–0.33∗1/2)). Focusing on two cut-off points employed in the literature (£12000, £24000) (38, 39), adjuvant CMF in breast cancer appears to be cost-effective.

Sensitivity analysis

Although I would argue that the current study has followed a sound methodology for cost-utility and cost-effectiveness analysis, the model is based on different epidemiological and economic assumptions. A sensitivity analysis was therefore performed. This type of analysis allows the economist to compensate for assumptions that are made in the model that may not be known with certainty.

The drug costs may differ between clinics and countries. Even the use of brand-name products instead of generic products will inflate drug charges. Employing a cut-off by 10% of drug charge, the cost per life year saved (5% d.r.) would range between £2090 and £5657, depending on how the indirect costs are implemented.

Table 3

Treatment costs in adjuvant CMF using a Norwegian breast cancer model

	Cost/unit (£)	Courses	Cost (£)	Total cost (£)
Drugs[1)]				
Cyclophosphamide (900 mg)	11.0	9	99.0	
Methotrexate (60 mg)	11.9	9	107.1	
Fluorouracil (900 mg)	6.9	9	62.1	
Ondansetron (8 mg∗2∗2)	47.9	9	431.1	
Dexamethazon (20 mg∗1)	11.6	9	104.4	803.7
Drug administration				
Pharmacy[2)]	49.2	9	442.8	
Outpatient treatment[3)]	66.3	9	596.7	1 039.5
Travelling	10	9	90	90
Production loss[4)]				
£24 667∗0.35∗0.5 (Human capital approach)				
£24 667∗0.35∗0.5∗0.1 (Friction-cost approach)				4 320/432
Sum if human capital approach is employed				£6 253.2
Sum if the friction-cost method is used				£2 365.2

[1)] Dose is calculated according to a BSA of 1.73 m^2, a dose intensity of 85% and the included dose of 5-FU and cyclophosphamide was calculated in 50 mg intervals. The methotrexate dose was calculated to the nearest 5 mg step.
[2)] The tax per infusion prepared at the pharmacy was £16.4.
[3)] The tax for outpatient therapy includes the oncologists' and oncology nurses' fees.
[4)] Indirect costs. Annual cost per employed Norwegian (1996)∗number of CMF-treated women out of work for 6 months (%)∗employed (%) (∗0.1 in the friction-cost approach).

Another sensitivity analysis was performed to determine the cost-effectiveness if these women were not cured, but only lived half of their expected life-span (11.4 years instead of 22.4 years). The cost-effectiveness analysis then measured a cost per life year gained rising from £2170 and £5737 to £2843 (£2365/(0.39 + 5.2*0.085)) and £7516 (£6253/(0.39 + (5.2*0.085)), respectively. ACT consisting of CMF is still cost-effective.

Side effects causing hospitalization were not included in this analysis. The CMF regimens from the Milan trials (12) were not associated with any episodes of septicaemia requiring hospitalization. However, the ECOG study (40) was associated with a 2% sepsis rate. Assuming 2% of patients undergoing sepsis and hospitalization, the total cost will be raised by £89 using the value of DRG 416 (£4432—septicaemia age > 18 years). Other side effects of chemotherapy such as death due to therapy and secondary malignancies may have an influence on the need for hospitalization. However, new regimens like the CEF regimen (cyclophosphamide, epirubicin, fluorouracil) seem to be related more to a risk for secondary malignancy (acute leukaemia) than to CMF (16).

DISCUSSION

Patients undergoing adjuvant chemotherapy may be exposed to morbidity, with little gain in outcome. Therefore, a 'risk-benefit analysis' should be done before initiating any form of general systemic ACT. In this study, the cost per women treated with adjuvant CMF was £2365–£6253. In a cost-effectiveness and cost-utility analysis employing national as well as international data, the cost per life year saved and the cost per QALY (5% discount rate) were estimated to £2170–£5737 and £2973–£7860, respectively.

Løber et al. (30) calculated a cost of 14400 DKK (£1250) for 12 months of CMF therapy in 1988. During the 10-year period 1987–1997, the prices rose by 36% in Norway (Statistics Norway). Half of Løber et al.'s costs were incurred by drugs and drug administration and the other half by laboratory tests and physical examinations. Compared with our calculated cost for 6 months' CMF therapy (£2365–£6253) 10 years later, our results may seem quite expensive. However, this is due to the fact that the Danish study used a dose intensity of 59%. As argued (31, 32), I believe the estimate of a dose intensity of 85% can be achieved with support from today's new antibiotics and growth-stimulating factors. In the study by Irvin & Kuhn (21), the drug cost alone represented 40% of the total cost. They measured a cost per life year saved of US $1688 (about £1020) in 1992. This is in accordance with the 13–34% and £2170–£5737 (1998 price) calculated in our study. Although new chemotherapy drugs may be expensive, the administration costs are a more significant contributor to the amounts that have to be spent on ACT.

The following assumptions were made in this study: a) All women were calculated to be 50 years of age when ACT was initiated. This was necessary to determine the life expectancy of an individual. b) Women undergoing adjuvant CMF were considered to have the same life expectancy as those at same age if they had survived 10 years following therapy. This may be an optimistic assumption. However, as shown, when carrying out a sensitivity analysis calculating only half the expected life-span of these women (11.4 years instead of 22.4 years), ACT is still cost-effective.

The costs of all breast-cancer-related care after the episode of primary treatment may be missed by several readers. In principle, all costs related to breast cancer during the whole episode of disease should be considered. This means that all breast-cancer-related healthcare costs for the rest of the patient's life should be traced and compared with the two alternative strategies with or without ACT. However, this cannot be done without tracing patients' records from time of diagnosis to death. Although there are many imponderables, costs in added life years such as regular follow-up visits and hospitalization and terminal care costs can be assumed and implemented in a model. According to the recommendations from the NBCG (7), the great majority of patients are followed-up twice a year for 3 years and then annually for a total of 10 years. Mammography is recommended annually for women under 50 years of age and biannually for those aged 50 years or more. According to the Milan study (19), treatment with adjuvant CMF saved 0.51 years per person treated for the first 10 years. This indicates a mean raised cost of about a half year prolonged follow-up when ACT is employed (£62) (29). This cost occurs in a median time of 6 years following ACT and has to be discounted, making the value to be included about £46 (21). The cost of hospitalization and terminal care is the most difficult part in this assumption since I am not aware of any national data clarifying this topic. However, the median stay for cancer patients undergoing terminal care in the time period December 1996 to October 1998 at the Department of Oncology, University Hospital of Tromsø, was 10 days (41). The cost per day according to the Troms County Council (42) was £235, indicating a total cost of £2350 per patient given terminal care in hospital. However, the majority of patients are cared for at home or in nursing homes. Employing the suggested tax of the National Health Administration (43) of £108, the terminal care situation lasting for 21 days, the cost per patient can be estimated as £2268. When calculating 8.5% fewer patients undergoing terminal care, a median time of 6 years following ACT, the savings can be indicated £142 (21 days*£108*0.085*0.735). A corresponding Dutch study by Koopmanschap et al. (44) reported an average cost of terminal care in 1992 including home care, hospital care and nursing home care of Dfl 42700 (about £880) per

breast cancer patient with advanced disease. By implementing these assumptions in the cost-effectiveness analysis, the cost per life year saved can be reduced by about £65.

In this study CMF administered i.v. for 9 cycles every 3 weeks was calculated. However, CMF is reported in different versions. Most of the published data are based on the 'classical' CMF 1,8 regimen (10). Even the QoL data employed in this survey were based on results achieved with the classical CMF 1,8 (24). It can be argued that this study, incorporating the results of different CMF versions, does not follow a sound methodology. However, I believe there are only minor differences between the CMF regimens included.

Clinicians may be worried about this kind of analysis that clearly is important for unvalidated therapies. It may seem unnecessary in therapies that are universally recognized as the 'gold standard' in the treatment of breast cancer. However, this economic study documenting the cost-effectiveness of CMF could perhaps act as a guideline for future studies when new regimens are introduced. Today, new adjuvant regimens such as CEF (cyclophosphamide, epirubicin, fluorouracil) have been discussed (16). Today this regimen is standard practice in the USA. If CEF (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, fluorouracil 600 mg/m^2) is chosen instead of CMF, the total cost of adjuvant chemotherapy (9 cycles) alone, will increase from £268 to £383. Knowing the risk of cardiotoxicity and secondary leukaemia, a cost-effectiveness or cost-utility analysis of adjuvant CMF or CEF should be carried out.

Although the costs documented in this study seem affordable in North America and Western Europe, this is not the case world-wide. Abdyldaev et al. (45) reported that, for economic reasons, breast cancer patients in Kyrgyzstan could not afford ACT. The cost of CMF drugs per patient in Kyrgyzstan was calculated to be US $274, whereas the average monthly wages did not exceed US $50.

In summary, this study indicates that adjuvant CMF in breast cancer is a particularly cost-effective type of adjuvant chemotherapy that saves a significant number of life years at a reasonable price. Drug costs account for less than half of the total amount. When new adjuvant regimens are introduced in the future, cost-effectiveness analyses should be undertaken before initiating any new form of general systemic therapy. This study may be practicable as a model for such an analysis.

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