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Original Paper

Quality of Adjuvant Chemotherapy in Primary Breast Cancer in a Non-trial Setting. A Comprehensive Cancer Centre Study

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The quality of adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the compliance with guidelines for this treatment were studied in 323 premenopausal patients with node positive breast cancer, who were treated in the Comprehensive Cancer Centre East of The Netherlands (IKO) from 1988 to 1992, outside the setting of a clinical trial. The interval surgery–chemotherapy, the duration of chemotherapy, dose intensity (DI) and relative dose intensity (RDI) of CMF chemotherapy and validations of dose modifications were evaluated. 295 of 323 patients (91%) received adjuvant chemotherapy. CMF chemotherapy was used in 230 patients (78% of the chemotherapy receiving patients). The median time to the start of chemotherapy was 62 (range-35–139) days after surgery. Forty-two per cent of the patients finished their CMF chemotherapy within 168 days. Two per cent of the patients did not finish the six courses of CMF chemotherapy. The mean DI and RDI of the eligible patients in all CMF using hospitals were 80.4 ± 28.8% and 78.2 ± 28.4%, respectively. Aberrations of recommended guideline procedures resulted more often in suboptimal treatment than haematological toxicity. Adherence to the guidelines was variable and resulted in suboptimal adjuvant chemotherapy. The median follow-up of the patients treated in hospitals that agreed to the use of CMF was 5 years. The mean RDI of CMF in the eligible patients who relapsed was 72.2 ± 32.7%, compared with 81.4 ± 25.2% for the patients who did not relapse (P 0.01), suggesting a possible influence of the RDI on disease free survival. However, when the patients who did not receive chemotherapy were excluded, the mean RDI of the patients who relapsed was 85.0 ± 12.6% and of the patients who did not relapse 87.4 ± 12.6%, which was not significantly different (P = 0.20).

Key words: breast cancer, adjuvant chemotherapy, guidelines, compliance
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INTRODUCTION

THERE IS increasing awareness in cancer treatment that quality of treatment has impact on outcome. However, even in the framework of clinical trials, cancer treatment is not always given as indicated in the protocol [1]. Sometimes deviations are such that it may compromise treatment outcome. Outside of clinical trials little information is available on the quality of cancer treatment. One measure to ensure or to improve the quality of treatment is the use of guidelines. From the literature it is known that compliance with such guidelines is variable [2, 3].

In January 1988 the Comprehensive Cancer Centre 'Integraal Kanker Centrum Oost' (IKO), consisting of nine regional hospitals and one university hospital, circulated guidelines for the treatment of women with primary breast cancer. These guidelines were developed as evidence based guidelines and delegates from most of these hospitals, including radiologists, pathologists, surgeons, medical oncologists and radiotherapists consented to their content and use. The guidelines described indications for and the practical

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handling of adjuvant chemotherapy with six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) for premenopausal women with node positive primary breast cancer. During regular site visits of consultant teams from the Comprehensive Cancer Centre, all newly diagnosed breast cancer patients were discussed for diagnosis and treatment according to the guidelines. In November 1992 all involved physicians agreed to a retrospective review of the medical records of breast cancer patients by an external auditor to evaluate the compliance with the guidelines. The project started in June 1993. This report describes the results of this audit on 323 patients who were eligible for treatment according to the above-mentioned guidelines.

PATIENTS AND METHODS

All patients eligible for this review and treated from 1988 to 1992 were identified by two national registration systems: the IKO Cancer Registry, part of the Dutch Cancer Registry and by the pathology reports of the PALGA system (the national Dutch pathology registration system). From the patient records and files, the following items were registered: menopausal state, date of histology, date of surgery, dates of start and cessation of chemotherapy and the doses of CMF for each course of chemotherapy, including reasons for dose adjustment and delay.

The guidelines described the adjuvant cytotoxic treatment of premenopausal women surgically treated for axillary node positive primary breast cancer, Stage II to IIIa, according to the TNM classification of the UICC as confirmed in 1978. Chemotherapy should start as soon as possible after completion of surgery, at least within 28 days, and should be comprised of cyclophosphamide 100 mg/m^2 orally days 1–14, methotrexate 40 mg/m^2 intravenous days 1 and 8 and 5-fluorouracil 600 mg/m^2 intravenous days 1 and 8, every 28 days for a total of six cycles.

In case of myelosuppression, dose adjustments or postponements were recommended according to the following rules: at the start of the next cycle treatment was delayed for 1 week if white blood cells (WBC) $< 3\times10^9$/l and/or platelets $< 100\times10^9$/l. After 1 week delay or on day 8 of each cycle the dose was adjusted as follows: WBC $\geq 3\times10^9$/l and platelets $\geq 100\times10^9$/l, 100% CMF; WBC 2–3×10^9/l and/or platelets 75–100×10^9/l, 50% CMF; WBC $< 2\times10^9$/l and/or platelets $< 75\times10^9$/l: 1 week delay (day 1) or stop cycle (day 8). In case of stomatitis or conjunctivitis, chemotherapy should be discontinued temporarily, depending on the severity of the symptoms, not exactly specified by NCI or WHO toxicity grading. In case of renal impairment defined as a serum creatinine level > 150 μmol/l, methotrexate should be discontinued. In case of haemorrhagic cystitis CMF should be discontinued.

The timing of radiotherapy, if at all indicated, was at the discretion of the treating physician.

Dose intensity (DI) was defined as described by Bonadonna and Valagussa [4]. For each drug the total dose over all courses administered was divided by the total planned dose. The relative contribution of all three drugs was regarded by adding the DI of each drug and expressed as the DI of CMF by dividing this added percentage by three. Furthermore, the average relative dose intensity (RDI) was defined, depending on the number of courses given (n/6), the DI of all courses given of all three drugs and the total duration of the chemotherapy:

$$\mathrm{RDI} = \frac{n}{6} \times \left\{ \frac{\text{actual C}n}{\text{ideal C}n} + \frac{\text{actual M}n}{\text{ideal M}n} + \frac{\text{actual F}n}{\text{ideal F}n} \right\} \times \frac{4n\ (\text{weeks})}{\text{actual weeks}} \times \frac{100\%}{3}$$

in which n = the number of courses given. Actual Cn, Mn and Fn are the cumulative doses in mg given in n courses. Ideal Cn, Mn and Fn are the ideal calculated doses in mg in n courses as determined by multiplying body surface to advised guideline dosages.

Statistical analysis

Statistical analyses were performed using SPSS® software. An independent sample t test for means was used for the analysis of RDI of chemotherapy before and after June 1990 and for the analysis of mean RDI in the women who relapsed and who did not relapse. All reported P values are two tailed.

RESULTS

The number of evaluable patients and the number of patients who received chemotherapy are outlined in Figure 1. 323 women were eligible for treatment with adjuvant CMF chemotherapy according to the guidelines. 295 of 323 patients (91%) received adjuvant chemotherapy. CMF chemotherapy was used in 230 patients (78% of the chemotherapy receiving patients). 19 of these patients underwent a 3 instead of a 4 weekly schedule, with a methotrexate dose of 60 mg/m^2 intravenous days 1 and 8, while 5-fluorouracil and cyclophosphamide were given according to the guidelines. 5 patients (2%) did not finish their six courses of chemotherapy, 4 because of patients refusal or objective side-effects, 1 because of an intercurrent colon carcinoma with liver metastases.

In one hospital (hospital 3), which did not abide by the guidelines, six courses of a 3 weekly anthracycline-containing regimen were used for 65 patients instead of CMF. No duration of chemotherapy, no DI and RDI were calculated for these patients and no reasons for dose adjustments and delays were investigated.

28 patients (9%), 24 from the hospitals agreeing to CMF chemotherapy and 4 from the hospital using an anthracycline regimen, did not receive chemotherapy at all: 7 refused chemotherapy, 1 of these patients received hormonal therapy with tamoxifen instead. 13 patients were deprived of chemotherapy for various reasons, such as misinterpretation of minimal metastatic disease in the axillary nodes (n = 3), incorrectly presumed postmenopausal state (n = 6), the psychological condition of the patient (n = 2) and mental retardation (n = 2). In 5 patients adequate evaluation of the menopausal status was never done; they were regarded as postmenopausal by their treating physician. For 3 patients no rationale for no treatment with CMF was found in the

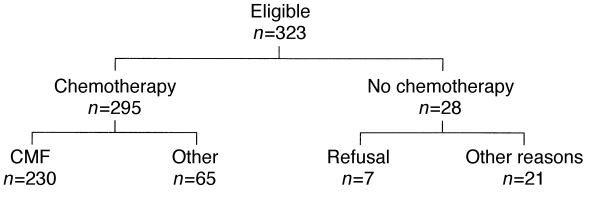

Figure 1. Numbers of eligible and evaluable patients for adjuvant chemotherapy. n = number of patients.

records, 2 of these patients were not discussed by the consultant team.

Interval between surgery and chemotherapy

3 patients moved before starting chemotherapy and in 2 patients the starting date of chemotherapy could not be found. The proportion of patients starting chemotherapy within the advised 28 days varied from 3% (1/30) in hospital 8 to 63% (41/65) in hospital 3. Only 26% (75/290) of all patients received their first chemotherapy within 28 days after surgery. The mean and median intervals between surgery and the start of chemotherapy for all patients were 58.7 ± 31.5 days and 62 (range 35–139) days, respectively. Patients without and with radiotherapy had a median time to the start of chemotherapy of 31 (range 12–108) and 75 (range 35–139) days, respectively. In most hospitals (1, 4–10) radiotherapy preceded chemotherapy. In two hospitals (2 and 3) these therapies were given simultaneously.

Duration of CMF chemotherapy

The duration of CMF chemotherapy could not be calculated in 6 patients because the data were unavailable (3 moved, 3 stopping date unknown). According to the guidelines, the ideal duration for CMF chemotherapy is 168 days. Forty-two per cent (94/224) of the patients finished their chemotherapy within 168 days. The variation between the hospitals was substantial, from 9.5% (2/21) in hospital 9 to 80% (16/20) in hospital 2. For all patients the median duration of CMF chemotherapy was 175 (range 70–259) days. Only hospitals 2, 5 and 10 had a median chemotherapy duration close to the expected minimal duration, 168, 163 and 170 days, respectively. However, this ideal duration of CMF chemotherapy was the result of guideline violations and not a reflection of adequate protocol adherence. In hospitals 2 and 10 delay for bone marrow toxicity with WBC < 3.10^9/l was often replaced by a not recommended dose reduction at the start of the subsequent course or in the second week of chemotherapy; in hospital 5, 19 patients started on a 3 instead of a 4 weekly regimen of CMF (therapy free interval 1 instead of 2 weeks) and in hospital 10 delay was often replaced by dose reduction.

DI and RDI of CMF chemotherapy

In the hospitals agreeing to CMF treatment, 254 (230 + 24) patients were eligible for CMF. The DI and RDI of the 24 patients eligible for CMF who did not receive chemotherapy were defined 0%. The DI and RDI (Figure 2) could be calculated for 247 patients. For 7 patients no DI and RDI could be calculated because of moving (3), chemotherapy given outside the region (1) and missing patient records (3).

The mean and median DI of all hospitals were 80.4 ± 28.8% and 92.3 (range 0–108.6)%, respectively. 39 patients (16%) had a DI less than 65%, 41 patients (17%)

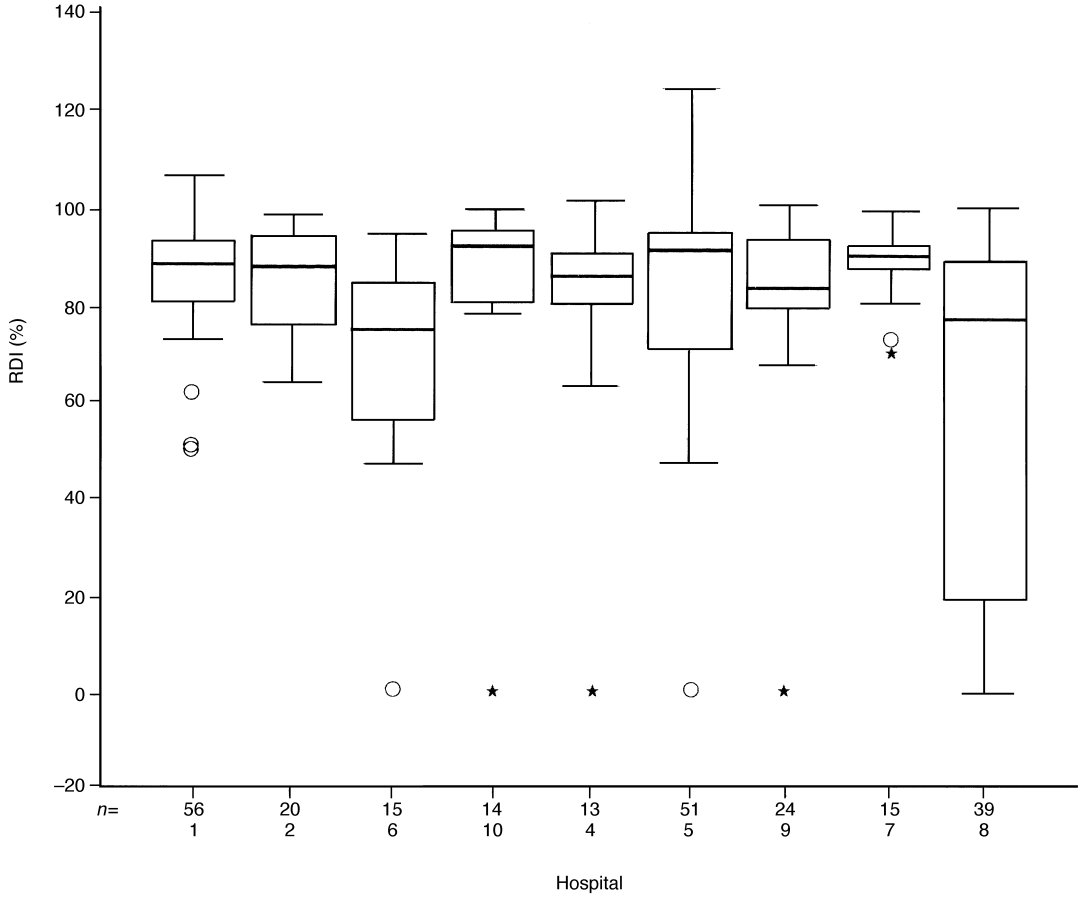

Figure 2. Relative dose intensity (RDI) of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy. Boxes indicate interquartile range (25–75%). Error bars indicate largest and smallest values that are not outliers. The horizontal line within each box is the median value. *, extreme value (>3 box lengths from the upper or lower edge of the box). ○, outlier (1.5–3 box lengths from the upper or lower edge of the box).

Table 1. *Reasons for delay and dose adjustments of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy*

		Bone marrow toxicity *n* (%)		Epithelial toxicity *n* (%)		Other reasons *n* (%)	
Hospital	Patients *n*	Delay*	Dose* adj.	Delay*	Dose* adj.	Delay*	Dose* adj.
1	56	29 (52)	25 (45)	0 (0)	7 (12)	9 (16)	26 (46)
2	20	2 (10)	2 (10)	1 (5)	0 (0)	4 (20)	17 (85)
4	11	2 (18)	3 (27)	0 (0)	0 (0)	4 (36)	7 (64)
5	44	6 (14)	11 (25)	1 (2)	2 (5)	32 (73)	33 (75)
6	13	9 (69)	3 (23)	1 (8)	0 (0)	10 (77)	11 (85)
7	15	5 (33)	3 (20)	0 (0)	1 (7)	9 (60)	12 (80)
8	29	8 (28)	4 (14)	1 (3)	1 (3)	22 (76)	24 (83)
9	21	17 (81)	0 (0)	1 (5)	0 (0)	16 (76)	15 (71)
10	13	2 (15)	3 (23)	0 (0)	1 (8)	7 (54)	13 (100)
ALL	222	80 (36)	54 (24)	5 (2)	12 (5)	113 (51)	158 (71)

n, number of patients; adj., adjustment. *Number of patients who had for the indicated reasons at least one delay or dose adjustment. Hospital 3 used an anthracycline-containing schedule for which no data on dose adjustments and delay were registered. This hospital was therefore excluded from the table.

had a DI between 65 and 85% and 167 patients (68%) had a DI of 85% or more.

The mean RDI (Figure 2) varied from 61.3 ± 38.2% in hospital 8 to 88.9 ± 8.1% in hospital 7. For all CMF-using hospitals the mean and median RDI were 78.2 ± 28.4% and 86.4 (range 0–125.1)%, respectively. The mean RDI for patients treated before June 1990 (74%) was lower than for patients treated after this date (81%), but this difference was not significant ($P = 0.06$). The RDI was considered good if $\geq 85\%$, moderate if between 70% and 85% and poor if $< 70\%$. A poor RDI was found in 0% up to 47% of the patients in hospitals 7 and 6, respectively. A good RDI was found in 27% in hospital 6 up to 80% in hospital 7. Seventeen per cent of all patients had a RDI $< 70\%$, whilst 53% of all patients had a RDI of $\geq 85\%$. If the patients who did not receive chemotherapy are excluded, 8.1% of the patients had a RDI of $< 70\%$ and only 59% of the patients had a RDI of $\geq 85\%$.

Up to June 1995, after a median follow-up duration of 5 years, 86 of 247 patients in whom a DI and RDI could be calculated relapsed. The mean DI and RDI of adjuvant CMF therapy in the 161 patients who did not relapse were 83.0 ± 25.6% and 81.4 ± 25.2%, respectively; the mean DI and RDI in the 86 patients who did relapse were 75 ± 33.7% and 72.2 ± 32.7%, respectively, which was significantly different (for DI $P = 0.05$ and for RDI $P = 0.01$). When the 24 patients who did not receive CMF chemotherapy were excluded, the mean DI and RDI of the 150 patients who did not relapse were 89.1 ± 12.5% and 87.4 ± 12.6%, respectively, and of the 73 patients who relapsed were 89.0 ± 11.3% and 85.0 ± 12.6%, respectively, and the differences were no longer significant for DI ($P = 0.96$) and for RDI ($P = 0.20$). 13 of the 24 patients who did not receive CMF chemotherapy relapsed.

Dose reduction and delay during CMF chemotherapy (Table 1)

Information could be obtained for 222 of the 230 women treated with CMF. In every woman dose adjustment or delay might have occurred more than once and different reasons for delay or adjustment were possible during chemotherapy. All items were scored yes if delay or dose adjustment occurred at least once. From Table 1 it is clear that the number of patients with one or more postponements or dose reductions of chemotherapy due to bone marrow toxicity varied considerably. The extreme high proportion of patients with bone marrow toxicity in hospitals 6 and 9 was due to the fact that blood control was carried out 2–4 days before the planned course of chemotherapy. Renal toxicity was encountered in 1 patient. Mucositis was a minor reason for dose adjustments and postponements, but a large number of patients had adjustments in timing and dose of chemotherapy for other reasons.

The reasons for delay and dose adjustment not due to bone marrow, epithelial or renal toxicity as mentioned in the guidelines were divided into valid and invalid reasons (Table 2). In total, 25 valid reasons for delay and seven for dose adjustment were counted, in contrast with 107 invalid

Table 2. *Number of valid and invalid reasons other than bone marrow toxicity or epithelial toxicity for delay and dose adjustment during cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy in 222 patients**

	Delay	Dose adjustment
Valid		
Complications of radiotherapy	6	1
Fever and/or symptoms of infections	16	5
Carcinoma of the colon	1	0
Second primary breast carcinoma	1	0
Cyclophosphamide cystitis	1	1
Invalid		
Concomitant or recent radiotherapy	3	7
3.0×10^9/l < WBC < 3.2×10^9/l	12	29
Calculation and administrative faults	–	77
Subjective complaints	1	7
Dose adjustment instead of delay	–	27
Delay instead of dose adjustment	8	–
Patient's request	10	3
Hospital logistics	13	1
Unknown reasons	28	39
Dose intensification by no delay or dose adjustment while WBC < 3.0×10^9/l	13	18
Courses with 3 instead of 4 weeks	19	–
Dose intensifying calculation faults	–	16
Total	132	231

*Number of different reasons for delay other than bone marrow toxicity or epithelial toxicity in 113 patients and number of different reasons for dose adjustment other than bone marrow or epithelial toxicity in 158 patients (see Table 1, columns 7 and 8). WBC, white blood cells.

reasons for delay or shortening of course interval and 224 for dose reduction or dose escalation.

DISCUSSION

In this study we found that the quality of adjuvant chemotherapy with CMF for breast cancer patients given outside the setting of a clinical trial is variable. Despite the fact that guidelines were used to assure the quality of treatment, the adherence to the guidelines varied considerably in the different hospitals.

Only 9% of the patients were deprived of adjuvant chemotherapy. Inaccurate menopausal state determination was the main reason. This result is probably due to the Dutch organisation of cancer care: The Netherlands is divided up into nine Comprehensive Cancer Centres, which are umbrella organisations to optimise the treatment of cancer patients by physician and nurse education, for example through the generation of guidelines and supplying information to patients. Consultant teams from the Cancer Centres discuss all cancer patients with the local oncology specialists. These consultations are based on the guidelines, leading to improved implementation by continuous medical audit. Our results contrast with reports from England and Italy: Chouillet and colleagues reported deprivation of chemotherapy in 36% of the premenopausal stage II breast cancer patients in south-east England [5], whilst Sainsbury and associates reported a doctor-dependent chemotherapy delivery from 0 to 46% for the Yorkshire region, unfortunately not specifying for menopausal state and breast cancer stage [6]. In Italy, Liberati and colleagues found that 78% of the premenopausal node positive breast cancer patients received chemotherapy, but of these patients 35% did not complete the six courses of chemotherapy [7].

Some studies on sequencing of chemotherapy and radiotherapy in primary breast cancer have reported an adverse effect in disease free and overall survival due to postponement of chemotherapy for radiotherapy [8–10], whilst concomitant chemotherapy and radiotherapy often resulted in a reduction of DI of chemotherapy [11] and an increased incidence of radiotherapy-related complications [12, 13]. It has also been stated that delay of radiotherapy after surgery results in more local recurrences and an increased rate of distant metastases [10, 14, 15]. In our population, radiotherapy preceded chemotherapy or was given simultaneously. This resulted in a median interval between surgery and the start of chemotherapy of 62 (range-35–139) days. The group of patients who did not need radiotherapy had a median interval of 31 days, much shorter than the 52 days mentioned in the randomised trial on this subject of Recht and colleagues [16] in the chemotherapy first group. The patients who underwent radiotherapy had a median interval of 75 days, which is shorter than the 119 days in Recht's radiotherapy first group, but longer than the chemotherapy first group. Recht and colleagues found more distant metastases in the delayed chemotherapy group compared with the chemotherapy first group, albeit with borderline significance. However, in the studies in which a decreased disease free survival due to chemotherapy delay is reported, this delay often exceeded 120 days. Knowledge of optimal timing of radiotherapy as well as chemotherapy within these 120 days after surgery was not available. The numbers of patients in our study who received concomitant chemotherapy and radiotherapy was too small to evaluate the influence on dose intensity or complications.

The DI results in our study are better than those of the trial of Bonadonna and associates [17], who reported on adjuvant CMF chemotherapy, with a DI less than 65%, 65–84% and more than 85% in, respectively, 34%, 45% and 20% of the patients. However, one has to take into account the fact that Bonadonna's trial started in 1973 and intended to give 12 cycles of CMF and that 50% of the treated patients were postmenopausal women. In 1994 Wood and colleagues reported that, in a randomised trial conducted with three different DI levels of adjuvant chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil, overall 95% of the patients received at least 90% of the assigned dose [18].

A good RDI of more than 85% for chemotherapy was reached in more than half of the patients in six hospitals, whilst in four hospitals a RDI less than 70% was found in 23–47% of the patients, which is a fairly large part of the study population. The DI and RDI are quick measures of treatment quality, although high DI and RDI can sometimes be generated by abnormal treatment schedules and low DI and RDI can be achieved by adequate treatment, hampered by toxicity.

DI is considered to be of importance for the results of chemotherapy in terms of disease free survival and overall survival [17, 18]. Although the DI and RDI of adjuvant CMF in patients who relapsed were statistically significantly lower than in patients who did not relapse, when those patients who did not receive adjuvant CMF chemotherapy were excluded, significance was not reached. Further analysis of these data needs to confirm the predictive value of the DI and RDI of adjuvant CMF in patients with primary breast cancer, but it is clear from our results that not giving CMF had an important influence on the relapse rate, which emphasises the importance of giving adjuvant chemotherapy to every eligible patient.

The reasons for suboptimal treatment in this study were numerous, and mainly unnecessary. Bone marrow toxicity was the only important therapy-related valid reason for dose modifications. Conspicuously, this varied in the different hospitals, most likely due to the fact that blood sampling time differed. Measuring WBC and platelets on the day of the planned chemotherapy could probably avoid delay or dose reduction. A pitfall in our study is the fact that haematological counts were not registered per cycle, so that it could be that, for example, in hospital 1 which had a high proportion of delays and dose reductions due to bone marrow toxicity these adjustments occurred only once in every patient, whereas in hospital 8 numerous delays or reductions took place in the course of treatment of 1 patient (see large variation in RDI in Figure 2). The other reasons for suboptimal treatment were mainly due to inaccurate guideline adherence and calculation faults.

This study confirms the doubts raised by Audet and colleagues that local therapy policies are not always comparable to the ideal standards as recommended in large clinical trials [19]. Reasons for this could be a much broader interpretation of guidelines than of a clinical trial protocol, leading to numerous different, mostly invalid and avoidable reasons for delay or dose reductions and even shorter courses and dose escalations. Interviews determined that the variation in adherence in our study was in part due to the fact that not all treating specialists were personally involved in the generation of the guidelines. The method used to develop these guidelines was most closely related to the model advocated by the American College of Physicians [20]. In this model, an expert

reviews the literature and presents a set of recommendations. After this proposition, the practitioners give their opinion which is also incorporated into the guidelines. In the development of the presented guidelines only deputies with different specialist backgrounds from the different hospitals gave their opinion. It probably would have been better to involve all specialists who administer chemotherapy in the generation of the guidelines, as first published by Park and associates [21]. Nevertheless, it is known that even though guidelines are supported by all practitioners, this may not result in implementation of the recommendations [3]. Repeated medical audit, checklists and toxicity grading systems and reports on RDI, the interval between surgery and chemotherapy and the reasons for delay and dose adjustment will possibly lead to further improvement [1]. A study using a decision tree on surgery and pathology reports and standardised estimation of menopausal state to prevent patients being excluded from chemotherapy on the basis of invalid reasons, in combination with chemotherapy guided by a toxicity symptoms checklist and advice in case of toxicity and DI reporting is ongoing in our region.

In conclusion, the quality of adjuvant chemotherapy with CMF for breast cancer patients was studied by evaluating five aspects: the interval surgery–chemotherapy, the duration of chemotherapy, DI and RDI and validations of dosing schedule modifications. For 74% of the patients, chemotherapy was delayed longer than 28 days, the median duration of chemotherapy was 175 (range 70–259) days, the mean DI and RDI were $80.4 \pm 28.8\%$ and $78.2 \pm 28.4\%$, respectively, the reasons for dose reduction or delay were often not due to treatment toxicity. Our data indicate that compliance with guidelines is variable and might result in a reduction in administered therapy and compromised outcome. This emphasises the important role of a system which enhances accurate treatment delivery in day to day care. The fact that the vast majority of patients are treated outside the framework of either protocols or guidelines further emphasises the relevance of our findings for both patient and treating medical oncologist. The adequate delivery of proven medical approaches, such as adjuvant chemotherapy in breast cancer patients, might be even more relevant than the introduction of certain new approaches.

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