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Dose Intensity of Chemotherapy with Cyclophosphamide, Methotrexate and 5-Fluorouracil in the Elderly with Advanced Breast Cancer

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Toxicity and results of two different dose levels of chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in older (> 70 years) patients with advanced breast cancer were evaluated in a prospective (non-randomised) study. During the first three courses of chemotherapy dose reduction for haematological toxicity was necessary in all of 10 and 8 of 13 patients treated with an intended dose of 100% and 75% of standard dose CMF, respectively. The median percentages of CMF, administered during the first three courses were about 75% in both groups of patients corresponding with a median dose intensity of 72% (range 49–87%) and 64% (range 36–78%) for patients of the 100% and 75% dose group, respectively. In 34 younger postmenopausal women (mean age 57 years) treated in our institution for advanced breast cancer the median percentages of CMF in the second and third course were 86% and 84%, respectively with a median dose intensity during the three courses of 82%. Dose reductions of CMF and bone marrow toxicity, though interdependent, were statistically significantly correlated with the endogenous creatinine clearance, but not with age. 1 patient died during severe leukopenia and thrombocytopenia. Non-haematological side effects were most pronounced in the 100% group. Results of therapy in both groups of patients were about equal and compared well with those of CMF therapy in general. It is advised that the dose of CMF in patients above 70 years should not exceed 75% of standard dose. Further dose reduction of methotrexate in case of severe renal failure is required.
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INTRODUCTION

IN WESTERN countries the incidence of breast cancer steadily increases with age [1]. Together with the increase of the number of older women, the number of older patients with primary and advanced breast cancer is rising [2]. Older patients with advanced breast cancer more often have tumours with positive receptor activity for oestradiol (OER) and progesterone (PgR) than younger ones [3,4] and therefore frequently will favourably respond to endocrine therapy [5]. However, ER- and PgR-activities are negative in about 25% of advanced breast cancer patients over 70 years of age [3–5]. These patients and those, not (longer) responding to endocrine therapy, might be candidates for chemotherapy. It has to be considered that in older people both the tolerance for, as well as the metabolism and excretion of cytostatic drugs are decreased [6, 7]. Furthermore, older people frequently have additional medications, easily leading to deleterious drug interactions [7]. Doses of chemotherapy should be optimal to gain maximal benefit of therapy [8, 9].

One of the mostly used chemotherapeutic regimens for patients with advanced breast cancer is the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). In this paper the toxicity and side effects as well as the results of CMF treatment given with an intended dose of 100% or 75% of standard dose in the elderly with advanced breast cancer (i.e. over the age of 70) will be discussed.

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PATIENTS AND METHODS

CMF-chemotherapy

The data of 23 consecutive patients with advanced breast cancer over the age of 70 years and treated with CMF were analysed. CMF chemotherapy was given for symptomatic and progressive disease not suitable for endocrine therapy. Regarding standard doses for CMF (cyclophosphamide = 100 mg/m^2 orally day 1–14, methotrexate = 40 mg/m^2 intravenously day 1 and 8 and 5-fluorouracil = 600 mg/m^2 intravenously day 1 and 8, courses to be repeated every 28 days) patients were treated with an intended dose of all cytostatics of 100% of the standard dose (group 1, n = 10) or with an intended dose of 75% (group 2, n = 13). In group 1 the upper age limit was 77 years. The group of 34 younger postmenopausal women (mean age 57, range 45–70 years) were treated within the scope of EORTC trial 10852 [10] with an intended dose of 100% of all cytostatics.

During further therapy, treatment was postponed for one week if at the beginning of a new cycle, the leucocyte count was below 3×10^9/l and/or the thrombocyte count below 100×10^9/l. Otherwise, doses of cyclophosphamide, methotrexate and 5-fluorouracil in each half cycle were adjusted to bone-

Table 1. Dose reductions of cyclophosphamide, methotrexate and 5-fluorouracil according to the number of leucocytes and thrombocytes, before each half cycle

Leucocytes* ($\times 10^9$/l)	Thrombocytes* ($\times 10^9$/l)	Doses in each protocol (%)
> 3	> 100	100
2–3	75–100	50*
< 2	< 75	0

* At the first half cycle postponed for 1 week and adjusted thereafter.

marrow toxicity according to the data in Table 1. If during any cycle the lowest measured count was < 10^9/l for leucocytes and < 50 × 10^9/l for blood platelets, cyclophosphamide, methotrexate and 5-fluorouracil doses were further reduced by 25%.

Data analysis

Besides clinical factors as age and performance status [11] the following items of all individual patients were collected or calculated: endogenous creatinine clearance (ECC), calculated according Cockroft *et al.* [17]: ECC = [140 − age (years)] × weight (kg) × 0.85 × 1.23/serum creatinine level (μmol/l), in ml/min (modified for serum creatinine levels in μmol/l instead of mg/100 ml); the mean of the received percentages of the standard doses of cyclophosphamide, methotrexate and 5-fluorouracil during the complete and the first and second parts of course 1–3; dose intensity during three courses, calculated as mean % CMF-dose × 6 or 10 (weeks)/the number of actual weeks in which two or three courses of chemotherapy were completed; the values of leucocytes and thrombocytes during course 1–3; non-haematological toxicity, expressed according to WHO grade 0–4 [11].

Statistical analysis

Significance levels of correlations between two series of data were calculated by the Spearman rank correlation coefficient. Differences between two series of data were tested with the Wilcoxon two sample test and for survival times by the non-parametric test, developed by Gehan and Mantel. For qualitative relations the χ^2 test for contingency tables was used. All calculations were made using SAS (Statistical Analyzing System) statistical software [12].

RESULTS

The mean age of the 23 patients was [mean (S.D.)] 76 (4) years, range 71–89 years. Clinical characteristics of the 10 patients who were treated with an intended CMF dose of 100% of standard dose (group 1) and of the 13 patients who received an intended dose of 75% (group 2) are summarised in Table 2. 4 of the 23 patients stopped chemotherapy before the third course because of subjective toxicity (n = 2) or documented progression of disease. After course 2, 1 patient died due to sepsis.

Reduction of CMF doses during the first three courses

The mean percentages of standard dose of the individual drugs cyclophosphamide, methotrexate and 5-fluorouracil, administered during the first half course were 93, 90 and 91 in group 1, and 70, 72 and 75 in group 2, respectively. In Fig. 1 the median values of the mean percentages of CMF (from standard doses) of every individual patient administered during the first six half courses related to the intended dose level are given. The data of the younger patient group is included in Fig. 2, referring to the median dose levels during courses 1–3. It can be read from these figures that the median dose levels of CMF after the first half course were in the same range in both groups of the elderly and lower than 85% in the younger age group. Dose reduction was necessary in all of 10 patients of group 1 and in 8 of 13 patients of group 2, corresponding with dose reduction in 60% of 28 and 29% of 35 courses of CMF in each group, respectively (P = 0.02). For comparison, dose reduction was necessary in 24 of 34 younger postmenopausal women during the first three CMF courses, corresponding with 43 reductions during 100 cycles (P versus group 1 < 0.05). The median level of dose intensity during two to three courses was

Table 2. Clinical characteristics related to the intended CMF dose-level

	Intended CMF dose		
	100% (n = 10)	75% (n = 13)	P value
Mean age (S.D.) (years)	74 (2)	78 (4)	0.02
Range (years)	71–77*	71–89	
WHO performance			
0	—	—	
1	5	7	
2	4	5	
3	1	1	> 0.1
Median calculated			
ECC (ml/min)	59	51	> 0.1
Range (ml/min)	40–76	28–77	
Previous chemotherapy	1	2	

* Upper limit 77 years.

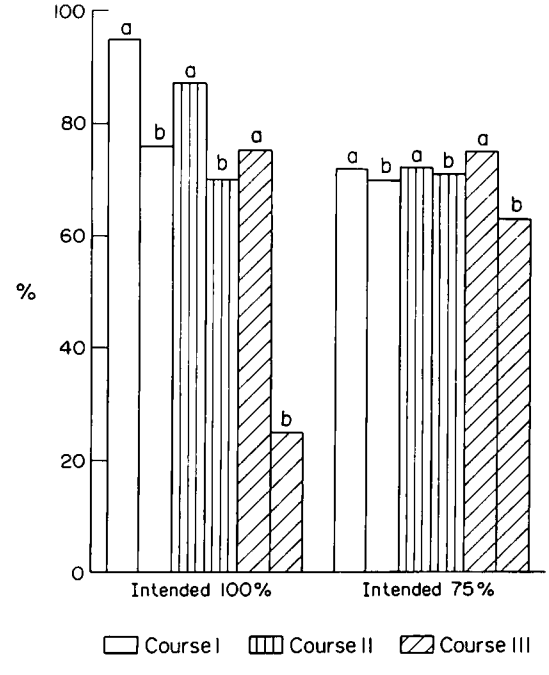

Fig. 1. Median values and ranges of the mean percentages of CMF (of standard doses) during three courses of chemotherapy related to the intended dose levels. a = First part, b = second part.

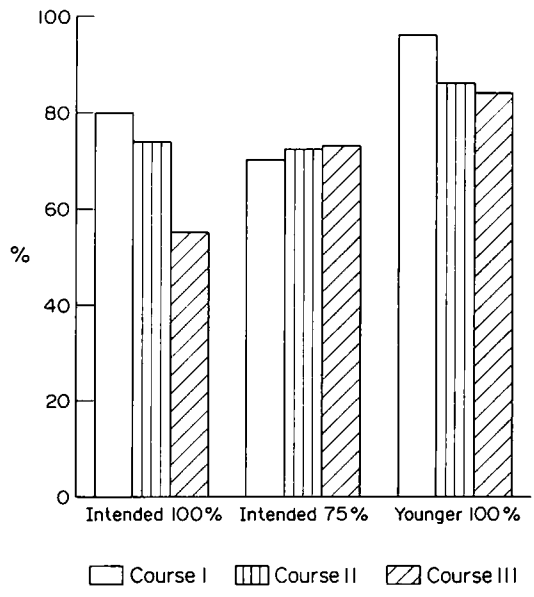

Fig. 2. Median values of the mean percentages of CMF (of standard doses) during three courses of chemotherapy related to the intended dose levels. Values of younger patients included.

72% (range 49–87%) and 64% (range 36–79%) for patients in group 1 and 2, respectively and 82% for the younger age group.

Dose reduction versus age

In 10 patients less than 76 years and 13 patients of 76 years and older reduction of CMF doses after the first half course was necessary in 48% of 29 and 38% of 34 courses, respectively ($P > 0.1$). Within group 1 and group 2 dose reduction was not related to age in these small groups of patients. In the younger age group dose reduction was necessary in 35% of 54 courses of patients below the age of 60 and in 52% of 46 courses in patients of 61–70 years ($P = 0.1$).

Dose reduction versus endogenous creatinine clearance (ECC)

The median of the calculated ECC's was 56 ml/min (range 77–28 ml/min). In 11 patients with an ECC below 56 ml/min and in 12 patients with an ECC above this level dose reduction of CMF was necessary in 63% of 27 courses and 28% of 36 courses, respectively ($P < 0.02$). In all 4 patients with an ECC below 40 ml/min dose reduction was given in 90% of 10 courses whereas in 13 of the 19 remaining women 34% of 53 courses had to be reduced ($P < 0.01$).

Haematological toxicity

In Table 3 the median values and ranges of the lowest measured numbers of leucocytes and thrombocytes during the first three courses of chemotherapy are given. The lowest values of leucocytes and thrombocytes did not differ significantly in groups of patients who received intended doses of 100% and 75% of standard dose CMF (it is stressed that dose reduction of chemotherapy mainly has been applied for haematological toxicity). In both groups, leukopenia below 10^9/l (grade 4) has been observed in 3 and 2 patients, respectively. Leukopenia below 2×10^9/l (grade 3 and 4) occurred in 43% of 28 courses and in 17% of 35 courses ($P < 0.05$) in 6 and 5 patients of group 1 and 2, respectively. Thrombocytopenia below 50×10^9/l (grade 3 and 4) occurred only in 2 patients who initially received 75% of CMF.

Table 3. Lowest measured leucocytes and thrombocytes counts during three courses of chemotherapy related to the intended dose levels

	Intended dose level 100%			Intended dose level 75%		
Course No.	I	II	III	I	II	III
Leucocytes*						
Median	3.3	2.0	2.2	2.9	3.3	3.4
Range	0.3–4.0	0.7–5.2	1.4–6.0	1.4–4.9	0.1–4.3	2.1–5.0
Thrombocytes*						
Median	164	143	148	157	115	120
Range	66–265	50–215	70–269	29–337	10–545	66–264

* $\times 10^9$/l.

Haematological toxicity in relation to age

When age of the patients and lowest leucocyte and platelet counts during the first course were correlated, no statistical significance was found (Spearman Rank correlation coefficient for age and leucocytes ($r = 0.15, n = 23, P > 0.1$); for age and thrombocytes ($r = -0.18$, $n = 23$, $P > 0.1$). However, the most severe leukopenia (0.1×10^9/l) and thrombocytopenia (10×10^9/l) occurred in the oldest patient (89 years) during the second and already mitigated course of CMF. This severe toxicity might have been provoked by accidental concomitant medication with trimethoprim-sulfa for urinary tract infection at an ECC of 38 ml/min.

Haematological toxicity and calculated ECC

Within the margin of 71–89 years no statistically significant (inverse) correlation between age and ECC was found ($r = 0.19$, $n = 23, P > 0.1$). Although there was no statistically significant association between the lowest values of leucocytes or thrombocytes and ECC, the decrease of the number of leucocytes during the first half of the first cycle was significantly correlated with the ECC ($r = -0.44, n = 23, P < 0.05$).

Blood transfusions

3 and 2 patients in groups 1 and 2 received a transfusion of erythrocytes after the haemoglobin levels decreased below 5.5 mmol/l.

Other side effects

Table 4 summarises toxicity in both groups of patients. Nausea/vomiting and mucous membrane toxicity was reported

Table 4. Toxicity (WHO grading)

	Intended CMF dose					
	100% ($n = 10$)			75% ($n = 13$)		
Grade	1	2	3–4	1	2	3–4
Nadir leucocytes*	1	3	6	4	4	5
Nadir thrombocytes	0	3	1	3	1	3
Infections	0	1	2	0	0	1
Mucous membrane	6	1	2	7	1	0
Nausea/vomiting	3	5	2	2	5	0
Alopecia	7	2	1	5	4	0
Thromboembolic			2			2

* The numbers refer to the actual number of patients.

by the majority of patients but was moderately severe or severe in 4 patients of group 1. 5 patients required a wig temporarily, although grade 3 alopecia occurred only in 1 patient of group 1. Infections, requiring antibiotic therapy occurred in 3 patients. One of these, the oldest woman of 89 years denied treatment of her infection and died by sepsis during severe leukopenia and thrombocytopenia. In 4 of 23 patients thromboembolic events, requiring anticoagulant therapy, were observed (calf vein thrombosis $n = 2$, pulmonary embolism $n = 1$ and non fatal myocardial infarction $n = 1$). Non-haematological side effects were more pronounced but did not differ significantly in groups of patients treated with an intended dose of 100% or 75% of standard dose CMF.

Results of therapy

9 of 23 patients had an objective remission with a median duration of 11 months (range 3–24 months). In 3 further patients the disease remained stationary during 7–9 months. Results in group 1 and group 2 were about equal (objective remission 4/10 and 5/13 patients, respectively). The median survival time of patients responding or failing to therapy was 27 months (range 3–39 months) and 8 months (range 2–21 months), respectively ($P < 0.01$).

DISCUSSION

All of 10 older patients who were treated with an intended dose of CMF of 100% of standard dose needed dose reduction during the first three courses of chemotherapy. Regardless of the intended initial dose (100% or 75% of standard dose CMF), the actual doses and dose intensities of CMF during the second and third course were in the same range and considerably lower than in a separate group of younger women treated with the same regimen. Notwithstanding the fact that doses of CMF were reduced mainly for haematological toxicity, severe (grade IV) leukopenia has been observed in 5 of 23 patients. Non-haematological side effects were more pronounced in the intended 100% group and not markedly different from those expected in younger women. Because the upper age limit of the group of patients treated with an intended CMF dose of 100% was far below that of the 75% group, extrapolation of toxicity of standard dose of CMF for all elderly suggest larger differences than we described. Carbone *et al.* [13] found that side effects of chemotherapy in the elderly in general have a similar spectrum as in younger patients but also noted that haematological toxicity was more pronounced in the elderly.

Within the relatively small range of ages (71–89 years) CMF toxicity was not significantly correlated with age. Gelman and Taylor [14] also found no correlation between CMF toxicity and age in patients above 70 years, although these authors calculated the doses of cyclophosphamide and methotrexate according to the renal function.

Increased toxicity of chemotherapy in the elderly might be due to a decrease in the repair capacities of involved organs, and to increased availability of individual drugs as a consequence of decreased albumin binding and/or delayed metabolism or excretion [6, 7]. Interactions with frequently used concomitant medications at old age may contribute as well [7]. It is well-known that the (duration of) the availability of methotrexate is strongly dependent on the rate of renal excretion [6, 7], the distribution into fluid containing body spaces and on the binding to serum albumin. In the small group of the older patients of this study, reduction of CMF doses (as expression of haematological toxicity) was statistically significantly correlated with ECC and can be best explained by the decreased excretion of methotrexate with decreasing ECC. The toxicities of cyclophosphamide and 5-fluorouracil are much less depending on the renal excretion of these drugs. The lethal toxicity in the oldest (89 years old) patient of this study during the second mitigated course of CMF might have been provoked by the concomitant use of trimetoprim-sulfa at an EEC of 38 ml/min. This drug is known to interfere with the excretion of methotrexate especially in the case of renal failure [7]. Drugs such as salicylate, other non-steroidal anti-inflammatory drugs and probenecid also are known to interfere with methotrexate excretion or with a decreased binding of this drug to plasma albumin [7].

In 4 out of 23 patients of this study thromboembolic complications, post or pre CMF chemotherapy, were diagnosed. An increased incidence of thromboembolic complications during chemotherapy has been reported earlier [15]. Careful monitoring for these complications in the elderly with often already existing vascular damage, is necessary.

The results of CMF chemotherapy in the elderly were in accordance with those in younger patients. In general, patients who acquired objective remission or stable disease had an increased quality of life despite the inconveniences of therapy.

CMF chemotherapy in women with advanced breast cancer over 70 years of age can be as effective as in younger ones, in our study there was an objective remission rate of 40%. On the basis of the recorded bone marrow toxicity and, therefore, need for dose reduction it can be estimated that the median dose of CMF that can be administered during the first three courses, hardly will exceed 75% of the standard doses. Further dose reduction of methotrexate is necessary in case of severe impaired renal function. Concomitant medication, interfering with the metabolism or excretion of methotrexate, should be avoided during the courses of chemotherapy. Thromboembolic complications may occur more frequently than in younger women.

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Parathyroid Hormone Related Protein and Skeletal Morbidity in Breast Cancer

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The presence of parathyroid hormone related protein (PTHRP) in human breast cancers has been assessed by immunohistochemistry using a polyclonal antiserum specific for the mid-region sequence 37–67 in an immunoperoxidase technique. The primary tumours from 155 normocalcaemic, consecutive women with early breast cancer who had been followed up for a minimum of 5 years were assessed. Dewaxed paraffin sections of formalin fixed tissue was used throughout. Positive PTHRP staining was detected in 56% of the cancers and was unrelated to standard prognostic factors, recurrence or survival. However, PTHRP positivity was related to the development of bone metastases ($P \leq 0.03$) and hypercalcaemic episodes. PTHRP is implicated as the humoral factor responsible for hypercalcaemia associated with breast cancer and tumour positivity may be a useful predictor of which women will develop bone metastases.
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INTRODUCTION

BONE METASTASES affect 70% of women with advanced breast cancer and cause considerable skeletal morbidity [1, 2]. Hypercalcaemic episodes occur in 10% of patients with bone metastases and are associated with a poorer survival [1–3]. Bisphosphonate therapy for bone metastases from breast cancer reduces skeletal morbidity when used in conjunction with hormonal or chemotherapy regimens [4]. Potentially bisphosphonates might be used in the early prevention of the morbidity associated with bone metastases but no good marker exists to predict when women are likely to develop skeletal metastases [4].

Parathyroid hormone related peptide (PTHRP), the putative cause of humoral hypercalcaemia of malignancy, stimulates bone resorption in animal models [5] and it has been suggested that the production of PTHRP by breast cancer cells may facilitate the development of skeletal metastases [6, 7]. The aim of this study was to determine the frequency of expression of PTHRP in human breast cancers by immunohistochemistry and its relationship to the subsequent skeletal morbidity experienced.

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PATIENTS AND METHODS

Patients

A consecutive series of 155 normocalcaemic women with early invasive breast cancer who were presented to Selly Oak Hospital from August 1984 to December 1985 were studied. None of the patients had clinical evidence of bone metastases at presentation and all were normocalcaemic. The upper limit of the reference range for corrected calcium is 2.65 mmol/l. The following prognostic factors were recorded on a computerised database:- age, tumour size (mm) and TNM stage, histological grade (modified Bloom and Richardson [8] method) and type, pathological lymph node status, oestrogen and progesterone receptor status, and menstrual status. Oestrogen and progesterone receptor status was measured using a dextran-coated charcoal method and Scatchard analysis [9]. Tumours containing hormone receptor levels $\geq$ 5 fmol/mg protein were considered steroid receptor positive. Menstrual status was classified by designating the patients as premenopausal (less than 12 months since last menstrual period) or postmenopausal (more than 12 months since last menstrual period, hysterectomised—ovariectomised or hysterectomised and 50 or more years of age). Patients were treated by either mastectomy with axillary clearance or node sampling (n = 97) or breast conserving operations (wide local excision and radiotherapy, n = 58). All patients were seen every