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"Classical" CMF versus a 3-weekly Intravenous CMF Schedule in Postmenopausal Patients with Advanced Breast Cancer

An EORTC Breast Cancer Co-operative Group Phase III Trial (10808)

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The "classical" CMF (cyclophosphamide/methotrexate/5-fluorouracil) schedule was compared with a modified 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer, as concern had arisen as to whether the classical schedule was the optimal way to give these drugs. The response rate with classical CMF was 48% compared with 29% for intravenous CMF ($P = 0.003$). Response duration was similar at 11 months, but survival longer for the classical schedule (17 versus 12 months, $P = 0.016$). We conclude that classical CMF is the superior regimen and attribute this to the higher dose intensity achieved.
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INTRODUCTION

By 1980, the "classical" CMF regimen (cyclophosphamide 100 mg/m^2 orally, days 1–14, methotrexate 40 mg/m^2 intravenously days 1 and 8, 5-fluorouracil (5-FU), 600 mg/m^2 intravenously days 1 and 8) had become a standard chemotherapy combination for the treatment of breast cancer in advanced disease and for adjuvant therapy. The rationale for the choice of the drugs was clear: they are three non-crossresistant drugs, each moderately effective as a single agent in advanced breast cancer.

The choice of the schedule was arbitrary, being analogous to the MOPP (mechloroethamine, vincristine, procarbazine and prednisone) schedule which had been very effective in advanced Hodgkin's disease [1]. The CMF schedule has been widely accepted as safe without unpredictable side-effects, easy to modify according to toxicity, and readily manageable in an outpatient clinic. In advanced disease a response rate of about 50% can be expected [2–4].

In the EORTC Breast Cancer Cooperative Group several aspects of the schedule had been the subject of discussions. A proportion of patients had problems taking the cyclophosphamide tablets for 14 days because of nausea and, sometimes, vomiting. This side-effect is more frequent with higher doses (150–200 mg daily). For many patients, quality of life was considerably reduced during the 2 weeks of cyclophosphamide use. Some patients reported they did not always take cyclophosphamide as prescribed. Hence, compliance with this agent given orally is uncertain. Variability in absorption of cyclophosphamide by the oral route could also lead to uncertainties in its bioavailability. There is little or no evidence to support that cyclophosphamide orally is best given over 14 days. Furthermore, administration of methotrexate and 5-FU on days 1 and 8 may not be optimal. For bone marrow recovery, it might be preferable not to use cyclophosphamide continuously for 2 weeks and not to repeat methotrexate and 5-FU on day 8. For these reasons, it seemed worthwhile to compare the effects of the classical CMF schedule with a 3-weekly intravenous CMF regimen, which had already been used in some centres. We report here a prospective randomised trial comparing these regimens for both efficacy and toxicity.

PATIENTS AND METHODS

Eligible patients were postmenopausal women (1 year or more after the last period) younger than 71 years with measurable and/or evaluable biopsy proven advanced breast cancer with evidence of progressive disease, having received no previous chemotherapy. Performance status was 2 or better (WHO) or 60% or more (Karnofsky index), white blood cells (WBC) $\geq 3 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l. The usual exclusion criteria were applied (UICC) [5, 6]. Patients with central nervous system (CNS) involvement were ineligible. Patients were randomised to receive either the classical CMF schedule (A), or modified 3-weekly intravenous CMF (B) (Table 1).

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Table 1. Trial design: randomisation to either schedule A or B

A (classical)	Cyclophosphamide 100 mg/m² orally days 1–14. Methotrexate 40 mg/m² intravenously days 1, 8. 5-fluorouracil 600 mg/m² intravenously days 1, 8. Repeat day 29.
B (modified)	Cyclophosphamide 600 mg/m² intravenously day 1. Methotrexate 40 mg/m² intravenously day 1. 5-fluorouracil 600 mg/m² intravenously day 1. Repeat day 22.

Dose modification schedule includes dose-escalation according to observed bone marrow depression (see Table 2).

Table 2. Dose reduction and escalation, according to blood count on day 1 (both schedules) and day 8 (schedule A only)

	Dose, all drugs
WBC (× 10⁹/l)	
> 4	125%
3–4	100%
1.5–3	50%
< 1.5	0
Platelets (× 10⁹/l)	
> 150	125%
100–150	100%
75–100	50%
< 75	0

Dose and dose modification

At the first cycle 100% dose was given (Table 1). If, at the beginning of further cycles, dose reduction was required, treatment was postponed for 1 week; after that treatment was started with reduced doses if necessary (Table 2). Dose adjustments at day 8 (schedule A) were made according to this schedule. Dose modification also allowed for dose-escalation, toxicity permitting (Table 2).

Duration of treatment

If there was progression after two cycles on schedule A or three on schedule B, treatment was stopped. In case of response or no change, treatment was continued until progression, subject to tolerability.

Other treatments

During the study period, no endocrine treatment was given. Local radiotherapy for symptomatic lesions was allowed, but was avoided for lesions being measured or evaluated for response. Fields of irradiation were kept as small as possible to avoid bone marrow depression interfering with the projected dose schedules.

Table 3. Patients randomised, eligible and evaluable

	Total	Arm A	Arm B
Patients randomised	332	164	168
Ineligible	78	39	39
Eligible	254	125	129
Inevaluable for response	21	11	10
Evaluable for response	233	114	119
Evaluable for toxicity	238	116	122

Table 4. Distribution of patients' characteristics in both trial arms for all eligible patients

	Schedule	
	A	B
Number eligible	125	129
Age (years)		
< 50	13	12
50–55	23	32
55–60	47	34
60–65	24	31
65–70	18	20
Years postmenopausal		
1– 5	41	41
6–10	41	34
11–15	24	28
16–35	16	24
Unknown	3	2
Dominant site of disease		
Soft tissue	36	33
Bones	36	40
Visceral	53	56
Prior radiotherapy		
No	28	20
Primary	45	49
Metastases	25	30
Both	25	30
Prior hormone therapy		
No	33	41
Yes	92	88
Performance status (WHO)		
0	34	35
1	61	63
2	24	24
Unknown	6	7
Oestrogen receptor status	54	66
Positive	30	37
Negative	22	26
Unknown	70	61

Evaluation of response

Critieria for evaluation of response, and categories of response were those of the UICC [5, 6]. Toxicity was recorded using the 5-point scale of the WHO [7]. All cases (hospital records, measurements, radiographs) were reviewed by two external reviewers.

Statistical considerations

Assuming that classical CMF gives a response rate of 50%, 137 eligible and evaluable patients were to be entered on each treatment arm to ensure that a decrease in response rate of 15% with the modified CMF regimen could be detected. Response rates were compared using the χ^2 test for the comparison of

Table 5. Response to treatment according to treatment group

CMF schedule	Response CR	PR	NC	PD	Early death	Total	CR + PR*
A	5	50	33	21	5	114	48%
B	2	32	27	53	5	119	29%
Total	7	82	60	74	10	233	

CR = complete response, PR = partial response, NC = no change, PD = progressive disease.
* CR + PR for A vs. B, $P = 0.003$.

proportions. Survival curves were calculated according to the Kaplan–Meier method and compared using the logrank test.

RESULTS

Between 1981 and 1984, 332 patients in total were entered in the study by eight institutions (Table 3). 78 patients were ineligible (39 in each study arm). The reasons for ineligibility were: performance status too low (24 patients), premenopausal (14), insufficient documentation (16), baseline WBC lower than 3×10^9/l (6), no measurable lesions (4), no progressive disease at entry (4), central nervous system involvement (4), prior CMF (3) and concomitant endocrine therapy (3). Of the 254 eligible patients, 21 were inevaluable for response to treatment (11 in arm A, 10 in arm B), because of insufficient documentation (15), change of therapy (2), treatment refusal (2), insufficient dose (1) and toxic death (1).

The distribution of patients characteristics in the trial arms for all eligible patients is shown in Table 4. They are well balanced for age, metastatic patterns, prior treatment, performance status and oestrogen receptors.

In Table 5, the response to treatment is shown. There was a significant difference in objective response rate in favour of classical CMF (48%) as compared to intravenous CMF (29%); ($P = 0.003$). Table 6 indicates that the response rates with the two schedules were similar in patients with dominant visceral disease, but different for soft tisuses and bones as dominant sites of disease. The 5 complete remissions (CR) with classical CMF were in soft tissue, while the two CRs with intravenous CMF were in patients with dominant visceral disease.

Duration of response (Fig. 1) was similar with both regimens, each showing a median response duration of about 11 months ($P = 0.324$). The time to progression in all patients (Fig. 2) was significantly longer in the classical CMF group ($P = 0.000$). Survival was also longer with classical CMF ($P = 0.016$); median survival was approximately 17 months in the group treated with classical CMF and 12 months in the intravenously treated group (Fig. 3).

Table 6. Objective response rate in each study arm according to dominant site of disease

CMF schedule	Dominant site of disease: Soft tissue	Bones	Visceral
A	69%	47%	33%
B	29%	26%	29%

Table 7. Observed toxicities for CMF schedule*

	A ($n = 116$)	B ($n = 122$)	Difference
Toxic death	0	1	
Cardiovascular death	1	1	
Leukopenia ($\times 10^9$/l)			
> 2.0	81	105	Lower with A ($P < 0.01$)
2.0–1.0	31	14	
< 1.0	4	3	
Thrombopenia ($\times 10^9$/l)			
> 50	113	118	
50–25	2	2	No difference
< 25	1	2	
Nausea/vomiting WHO grading			
0	10	5	
1	31	21	More with B ($P = 0.06$)
2	42	52	
3	27	41	
4	6	3	
Oral mucosa WHO grading			
0	78	99	
1	17	11	Less with B ($P = 0.03$)
2	18	9	
3	2	3	
4	1	0	
Alopecia WHO grading			
0	33	33	
1	10	31	Less with B ($P = 0.03$)
2	31	33	
3	41	23	
4	1	0	

* Only worst toxicity experienced by patients recorded.

Observed toxicities are listed in Table 7; there are significant differences between the two treatment arms, indicating more nausea and vomiting, but less mucosal toxicity and hair loss in the patient group treated with modifed (intravenous) CMF.

Dose modifications due to leukopenia and thrombopenia, and percentage of drug received (in comparison with protocol-dose), are shown in Table 8. With the classical CMF treatment, dose-reductions were more frequent whereas with the intravenous schedule treatment was more often postponed (for leukopenia of less than 3.0×10^9/l). Dose modifications due to haematological toxicity were more frequent with the classical treatment. The percentages of drugs received with respect to protocol doses were comparable in the two treatment groups (including dose escalations).

DISCUSSION

Comparison of the classical CMF regimen with the modified intravenous schedule in advanced breast cancer showed a significantly higher response rate with the former (48% vs. 29%;

Table 8. Dose modifications and percentage of drug received at first evaluation

		A: classical	B: intravenous
Dose modification			
Any reason			
None		4	24
Postponed		35	54
Reduced		66	36
Both		3	0
Due to haematological toxicity		93%	68%
% drugs received at evaluation (± 2 months)		2 cycles	3 cycles
	C	11	7
< 80%	M	12	9
	F	13	8
	C	26	26
< 90%	M	25	23
	F	22	23
	C	71	73
≥ 90%	M	71	74
	F	73	75
Total		108	106
> 100%	C	60	65
Dose escalation	M	67	65
	F	65	68

C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil.

$P = 0.003$). The response to the classical CMF used here is that expected for the regimen. The higher response frequency was also reflected in a longer time to progression and duration of survival; the duration of response of 11 months was equal with each schedule.

Haematological toxicity necessitated dose reductions more often with classical CMF, while delays were more common with the intravenous regimen. The percentage of the protocol doses received was lower with the classical CMF regimen, but a higher

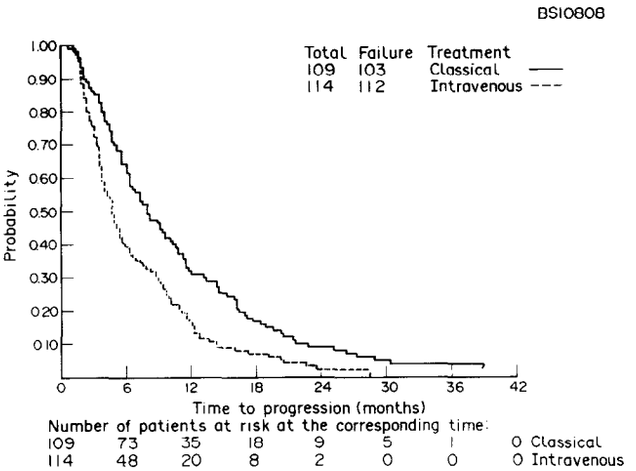

Fig. 2. Time to progression in patients on either classical or intravenous CMF. $P = 0.000$.

dose intensity per unit time was achieved with this schedule. Mucositis and alopecia were encountered more frequently with the classical schedule, while nausea and vomiting were more troublesome when all drugs were given intravenously.

The better results obtained with classical CMF can be attributed to the higher dose intensity achieved per unit time. Without dose modification, the classical CMF schedule after 8 weeks (two cycles) would have resulted in a dose of 2800 mg/m^2 cyclophosphamide, whereas with the modified schedule after 9 weeks (3 cycles) 1800 mg/m^2 would have been reached. For methotrexate, the total doses administered over the same period would have been 160 mg/m^2 and 120 mg/m^2 respectively and for 5-FU they would be 2400 mg/m^2 and 1800 mg/m^2 respectively. The question of compliance for patients taking the prescribed amount of oral cyclophosphamide has not been addressed in this study, but in the light of the present findings it appears not to be a significant problem.

We conclude that the classical schedule of CMF is more effective in advanced breast cancer than a modified intravenous schedule. The most plausible explanation for this is the higher

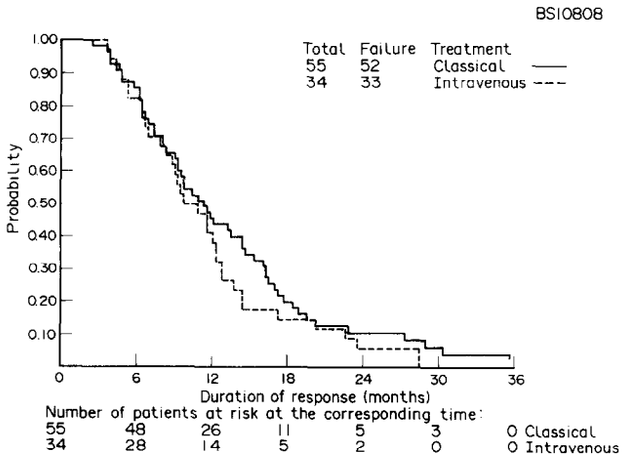

Fig. 1. Duration of response in patients on either classical or intravenous CMF. $P = 0.324$ (log rank).

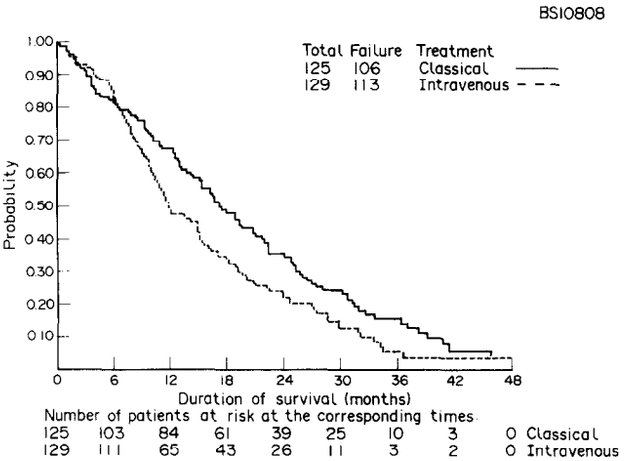

Fig. 3. Duration of survival of patients on either classical or intravenous CMF. $P = 0.016$.

dose intensity achieved with the classical regimen and this, together with its better tolerability, has important implications for the use of CMF as postoperative adjuvant systemic treatment for operable breast cancer.

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Prognostic Relevance of Cathepsin D versus Oestrogen Receptors in Node Negative Breast Cancers

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The concentration of total cathepsin D in cytosols of 199 node negative women with primary breast cancer in a 10-year retrospective cohort was assayed. Cathepsin D status alone was unable to predict disease-free or overall survival. However, those patients with receptor positive tumours who were cathepsin D positive had longer disease-free ($P = 0.02$) and overall survival ($P = 0.01$) than cathepsin D negative patients. Therefore, measurement of cathepsin D appears to provide additional prognostic information for the prediction of disease-free and overall survival in patients with node negative breast cancer.
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INTRODUCTION

OESTROGEN RECEPTOR STATUS has been used for over a decade as a prognostic index for node negative breast cancer patients. Its prognostic relevance has been consistently reported in many studies. Whereas it is clear that most oestrogen receptor negative (ER^-) patients will have recurrences, a smaller percentage of oestrogen receptor positive (ER^+) patients is also likely to have recurrences.

This emphasises the need for additional prognostic variables to discriminate the subset of ER+ patients at highest risk for recurrence. Several oestrogen-stimulated proteins and their proliferative activities have been studied, and increasing attention has been paid to an oestrogen-regulated protein first discovered as a secretion product from oestradiol-stimulated MCF-7 cells: cathepsin D, a 52 kD protein [1]. The protein seems to be a promising prognostic tool since its proteolytic activity might well be involved in the process of tumour invasion and metastatic spread.

In the present study we retrospectively analysed the impact of the presence of cathepsin D and oestrogen receptors on disease-free (DFS) and overall survival (OS) in 199 node negative breast cancer patients.

PATIENTS AND METHODS

Breast biopsy specimens were obtained from 199 patients with operable primary node negative breast cancer who entered the Istituto Nazionale Tumori between January 1980 and September 1983. The samples, collected at time of surgery of the primary tumour, were snap-frozen and stored in liquid nitrogen. There was histological confirmation of the diagnosis for all cases. None of the patients had any treatment before or after surgery until or unless there was a recurrence.

Tumours 2.5 cm or less in diameter accounted for 69.4% and those more than 2.5 cm in diameter for 30.5%. The median age of the patients was 51 years; 45.5% of the cases were

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