Pergamon

European Journal of Cancer, Vol. 33, No. 14, pp. 2321–2325, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)10011-9

Original Paper

Retreating Recurrent Breast Cancer with the same CMF-containing Regimen used as Adjuvant Therapy

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Breast cancer metastases appearing soon after adjuvant chemotherapy (within 12 months of its completion) are usually resistant to retreatment with the same cytotoxic agents, while relapses occurring later (beyond 12 months) regress when rechallenged with the same agents, showing similar response rates observed in non-pretreated patients with advanced disease. The International Breast Cancer Study Group (IBCSG) prospectively explored the efficacy of retreatment for patients upon relapse using the same therapy administered during the adjuvant programme. 87 patients previously treated with an adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) combination chemotherapy (with or without the addition of low-dose prednisone and tamoxifen), who had measurable first breast cancer relapse, usually after at least 6 months of completion of the adjuvant treatment, were treated with CMF. Pretreatment consisted of 1–3 CMF courses in 27 patients and 4 or more courses in 60 patients. 17 patients were retreated with additional tamoxifen or had tamoxifen stopped at relapse. The data of these patients are shown separately. 47 of the 86 fully evaluable patients (55%) had an objective response, which was complete in 25 (29%). The dominant metastatic type and the number of involved sites were the most important factors influencing response to retreatment. Patients with soft tissue metastases had a high response rate (36/52, 69%) compared with those who had visceral involvement (9/24, 38%) or those with bony disease (2/10, 20%) ($P = 0.002$). In conclusion, response rates to retreatment with CMF were similar to those expected in a non-pretreated population. The patterns of relapse and the number of metastatic sites were the most important factors predicting response to retreatment, while treatment-free interval (usually longer than 6 months due to the study design) did not influence response rates. This study supports the hypothetic effectiveness of late reintroduction of adjuvant cytotoxic therapy (prior to evidence of systemic relapse), upon which several current trials are based. © **1997 Published by Elsevier Science Ltd.**

Key words: recurrent breast cancer, chemotherapy
Eur J Cancer, Vol. 33, No. 14, pp. 2321–2325, 1997

INTRODUCTION

RELAPSES FOLLOWING primary therapy for breast cancer, even local recurrences in the scar of previous mastectomy, significantly impair prognosis. These events indicate that a potentially curable disease must be considered a chronic disorder without a significant chance for long-term freedom from disease.

Patients with early breast cancer commonly receive adjuvant systemic therapy as part of their primary treatment. Such a therapeutic approach leads to an improved survival when compared to delayed systemic therapy only given upon evidence of overt recurrence or metastases [1]. Unfortunately, many women who have received adjuvant systemic treatment eventually relapse, presumably due to resistance of tumour cells to the initial treatment programme. These cells survive during adjuvant systemic therapy.

The development of adjuvant therapies which might improve treatment outcome for women with operable breast cancer was typically based upon experiences from advanced disease. One of the most logical approaches of research in this field was aimed at reducing the emergence of drug-resistant

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Received 24 Oct. 1995; revised 24 Jul. 1997; accepted 30 Jul. 1997.

cells [2, 3]. Surprisingly, very few studies have compared the cellular, biochemical or genetic characteristics of breast cancer cells in the primary tumour with those of metastases appearing after adjuvant systemic treatment.

An understanding of why adjuvant systemic therapies often fail to control micrometastases would be advantageous for the development of new, more effective treatment approaches. Some evidence exists that prior adjuvant systemic therapy reduces the chance for tumour response (and duration of response) to systemic treatment given at the time of relapse. The average survival after relapse, which occurs subsequent to adjuvant systemic therapy, is shorter when compared with that of patients who had not received adjuvant therapies [4, 5]. This might imply that adjuvant treatments select resistant tumour cells which have a shorter doubling time. Studies of metastatic tumours appearing after completion of adjuvant therapy revealed that early relapses (within 12 months of completion of adjuvant therapy) are usually not sensitive to retreatment with the same cytotoxics [5]. However, if relapse occurred after such time lag, retreatment with the same drugs leads to similar response rates in pretreated and non-pretreated patients [6–8]. Such observations are the basis for the hypothesis that delayed failure of adjuvant systemic therapy (more than 12 months from its completion) might not be due to the emergence of drug-resistant cells, but rather to the inadequacy of the treatment in terms of sensitive tumour cell kill. This might be due to the persistence of non-dividing or dormant cells that survive adjuvant cytotoxics [9].

Several current adjuvant trials are evaluating the effects of late re-introduction of adjuvant therapy on potentially drug-sensitive cells hypothesised to have been dormant during the initial treatment. It is assumed that these cells will become vulnerable to cytotoxics by re-entering the cell cycle. Two different strategies might be used for implementing cell kill by re-introduced cytotoxics: increasing the time gap between initial and subsequent treatment by extrapolating the timing from models and attempting the recruitment of dormant cells into the cell cycle using oestrogen priming or growth factors. The latter approach is obviously not free of concerns due to a potential induced proliferation of tumour cells which are resistant to therapy [10].

The International Breast Cancer Study Group (IBCSG) explored, in a prospective study, the efficacy of retreatment for patients upon relapse using the same therapy which had been administered to them during the adjuvant programme. The assessment of response and survival for the study population of 87 patients is the subject of this report. Because many patients underwent additional surgical procedures following a chemotherapy-induced response, time to progression and response duration were not evaluated in this analysis.

Table 1. *Patients' characteristics at time of primary diagnosis*

	All patients	Patients without tamoxifen bias
Number of patients	87	70
Age (years)		
median	50	48
(range)	(33–70)	(33–66)
Ethnic group		
African	34	27
Caucasian	53	43
Menopausal status		
premenopausal	59	58
postmenopausal	28	12
Nodal status		
positive	81	64
1–3	36	30
4–10	27	19
> 10	18	15
negative	6	6
Oestrogen receptors (primary)		
negative (< 10 fmol/mg cytosol)	37	33
positive (≥ 10 fmol/mg cytosol)	44	31
unknown	6	6
Tumour size of the primary		
< 2 cm	5	3
≥ 2 cm	82	67
(> 5 cm)	(16)	(14)

PATIENTS AND METHODS

87 patients, at a median age of 50 years (range 33–70 years), previously treated in one of the adjuvant trials of the International Breast Cancer Study Group (IBCSG) [11–14] were accrued. All had been previously treated with a CMF (cyclophosphamide, methotrexate, 5-fluorouracil)-based chemotherapy, with or without the addition of low-dose prednisone and tamoxifen. All had to present a measurable first breast cancer relapse and had to have finished the adjuvant therapy programme at least 6 months before study entry. 3 patients (1 with bone metastases and 2 with loco-regional soft tissue manifestations) had an interval of 3–4 months and were considered eligible and evaluable, as we did not want to introduce additional bias in the patient selection. Due to the protocol requirement of having measurable disease, the selection of patients does not correspond to the usual relapse pattern in an adjuvant trial, but shows an excess percentage of patients with soft tissue recurrence. The treatment consisted of the same combination used in the adjuvant setting, and response was assessed using the WHO criteria.

17 patients received at relapse chemotherapy and additional tamoxifen (tamoxifen had been given initially for only 6 months) or had long-term tamoxifen stopped at relapse. Those patients were considered to have a potential bias, showing higher response rates due to tamoxifen or

Table 2. *Pattern of recurrence after completion of primary treatment*

Dominant metastatic site	All patients	Patients without tamoxifen bias
Total number of patients	87	70
Localisation		
soft tissue	52	43
bone	10	9
visceral	25	18
lung	15	11
liver	10	7
Number of involved sites		
1	61	51
≥ 2	26	19
Therapy-free interval (median)	21 months (range 3.2–143.6)	21 months (range 3.2–143.6)
up to 12 months	20 pts	17 pts
> 12–24 months	31	23
> 24 months	36	30

Table 3. Type and duration of previous adjuvant treatment

Adjuvant treatment	All patients	Patients without tamoxifen bias
Total number of patients	87	70
Short duration CT	35	35
CMF×1 (peri-operative)		
Prolonged duration CT	52	35
CMF×3	1	1
CMF×3 + CMF×3 (re-introduction)	4	2
CMF(± p)×6	18	17
CMFp×12	9*	9*
CMFp + T×6	16†	4‡
CMF×6 + CMF×3	1	1
T + CMF×3 (re-introduction)	3	1‡

*1 with additional oophorectomy. †2 with additional peri-operative cycle. ‡Retreated with CMF alone without tamoxifen. p, prednisone; T, tamoxifen.

tamoxifen withdrawal. The analysis was repeated separately for the 70 patients considered free from possible tamoxifen effect.

Table 1 (both for all 87 and for 70 patients without tamoxifen bias) shows the patients' characteristics. More than one third of the patients were African due to particular interest of the Cape Town institution in the trial. The majority had axillary node metastases at diagnosis and the tumour size at presentation was less than 2 cm for only 5 (3) patients. Table 2 presents the pattern of first disease recurrence at the time when the failed adjuvant systemic treatment was recommenced. The majority of patients had soft tissue recurrence and a small proportion had lung, liver or bone metastases. Seventy per cent of patients had only one metastatic site of disease. These patterns of disease are different from those in the entire population of patients who relapse after entry into IBCSG adjuvant trials [15]. In fact, the selection of patients for this retreatment study was limited to some institutions and was confined to patients with measurable disease.

Table 3 shows the randomised adjuvant treatments: 52 patients had received an adjuvant therapy consisting of at least three cycles of CMF [± low dose prednisone (p), or ± tamoxifen (T)], whereas 35 patients were pretreated with a single peri-operative course of CMF. 17 patients were retreated at relapse with the addition of tamoxifen, or tamoxifen was stopped at relapse just before starting the retreatment with CMF. Data are shown for the subgroup of patients for whom no tamoxifen (or tamoxifen withdrawal) response can be assumed. The majority of patients received several cycles of systemic therapy after relapse: 27 (22) patients received one to three cycles and 60 (48) patients recieved four or more cycles of treatment.

Differences in response rates (complete response + partial response) according to patient, tumour and treatment characteristics were assessed using Fisher exact tests. Survival from the time of initiation of chemotherapy for relapse was estimated by the Kaplan–Meier method and group comparisons were based upon the log-rank test.

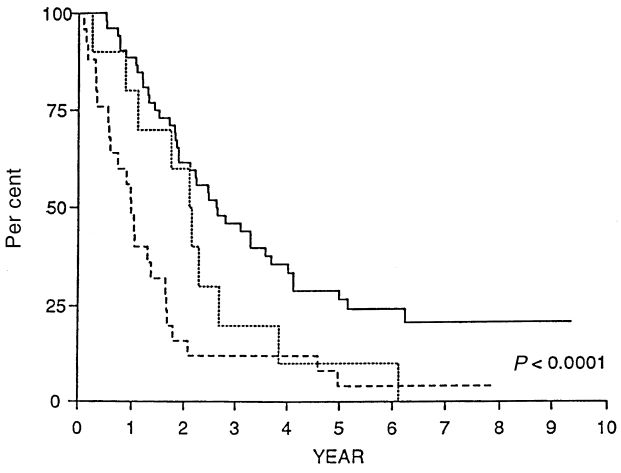
RESULTS

Table 4 shows the proportion of tumour responses observed with relapse therapy overall and according to patient, tumour and treatment characteristics for all patients and for the 70 patients without possible tamoxifen (or tamoxifen withdrawal) induced response. One postmenopausal patient with lung as the dominant metastatic site

Table 4. Results of treatment overall and according to patient, tumour and treatment characteristics

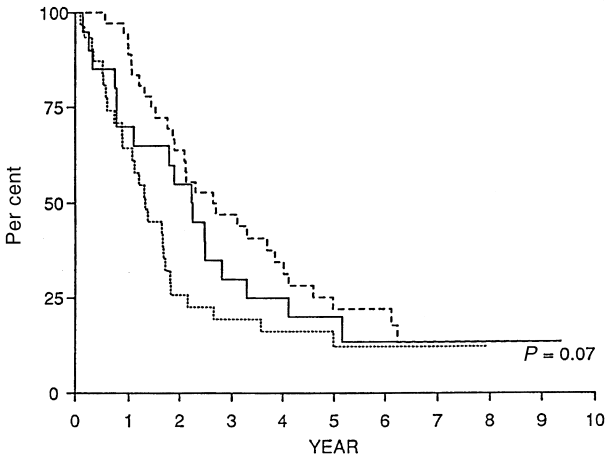
	All patients						Patients without tamoxifen bias					
	No. pts.	CR (%)	PR (%)	NC (%)	PD (%)	*P* value*	No. pts.	CR (%)	PR (%)	NC (%)	PD (%)	*P* value*
All patients	86	25 (29)	22 (26)	16 (19)	23 (27)		70	20 (28.5)	16 (23)	14 (20)	20 (28.5)	
Menopausal status												
premenopausal	59	15 (25)	14 (24)	13 (22)	17 (29)	0.16	58	15 (26)	13 (22)	13 (22)	17 (29)	0.25
postmenopausal	27†	10 (37)	8 (30)	3 (11)	6 (22)		12	5 (42)	3 (25)	1 (8)	3 (25)	
Dominent metastatic site												
soft tissue	52	22 (42)	14 (27)	8 (15)	8 (15)	0.002	43	19 (44)	10 (23)	6 (14)	8 (19)	0.002
bone	10	—	2 (20)	4 (40)	4 (40)		9	—	1 (11)	4 (44)	4 (44)	
visceral	24†	3 (13)	6 (25)	4 (17)	11 (46)		18	1 (6)	5 (28)	4 (22)	8 (44)	
lung	14	2 (14)	6 (43)	3 (21)	3 (21)		9	1 (11)	4 (44)	3 (33)	1 (11)	
liver	10	1 (10)	—	1 (10)	8 (80)		6	—	—	1 (17)	5 (83)	
No. of involved sites												
1	61	22 (36)	16 (26)	12 (20)	11 (18)	0.033	51	17 (33)	13 (25)	10 (20)	11 (22)	0.04
≥ 2	25†	3 (12)	6 (24)	4 (16)	12 (48)		19	3 (16)	3 (16)	4 (21)	9 (47)	
Therapy-free interval												
6–12 months	20	6 (30)	6 (30)	2 (10)	6 (30)	0.73	17	5 (29)	5 (29)	2 (12)	5 (29)	0.61
> 12 < 24 months	31	11 (35)	4 (13)	4 (13)	12 (39)		23	8 (35)	2 (9)	3 (13)	10 (43)	
> 24 months	35†	8 (23)	12 (34)	10 (29)	5 (14)		30	7 (23)	9 (30)	9 (30)	5 (17)	
Previous adjuvant treatment												
Peri-operative	35	13 (37)	5 (14)	6 (17)	11 (31)	0.66	35	13 (37)	5 (14)	6 (17)	11 (31)	1.0
Prolonged	51†	12 (24)	17 (33)	10 (20)	12 (24)		35	7 (20)	11 (31)	8 (23)	9 (26)	

*Fisher's exact test comparing CR + PR versus NC + PD. †One patient was not evaluable for response.



Site	Dead	Total	% 5-yr survival	(S.E.)
Soft Tissue	39	52	27	(6)
Bone	10	10	10	(9)
Viscera	24	25	4	(4)

Figure 1. Survival from start of relapse therapy according to dominant metastatic site for all 87 patients.



Interval (months)	Dead	Total	% 5-yr survival	(S.E.)
≤ 12	17	20	20	(9)
>12-24	27	31	12	(6)
> 24	29	36	22	(7)

Figure 2. Survival from start of relapse therapy according to therapy-free interval for all 87 patients.

and more than 2 involved sites, with more than 24 months therapy-free interval and long duration adjuvant therapy, could not be assessed for response and was excluded from the response analysis but included in the survival analysis. 47 of the 86 assessable patients (55%) had objective evidence of response and in 25 (29%) all measurable disease manifestations disappeared (complete response, CR). The response rates were similar (response rate 51.5%, CR 28.5%) when considering only the 70 assessable patients without possible tamoxifen-induced response.

The dominant metastatic type and the number of involved sites were the most important factors influencing response to retreatment. Patients with soft tissue metastases had a high response rate (36/52, 69%) compared with those who had visceral involvement (9/24, 38%) or those with bony disease (2/10, 20%) ($P = 0.002$). Similar results were seen in the 70 pts without tamoxifen bias. The response rate of patients with one metastatic site was significantly higher compared with patients with two or more sites ($P = 0.04$). These patterns of response are similar to those which have been reported in women who have had no adjuvant treatment and have received systemic therapy for the first time in the setting of metastatic disease.

The therapy-free interval did not significantly influence response rate. Furthermore, differences in response rate between patients who had previously received an adjuvant single course of i.v. CMF (peri-operative regimen) and those who had adjuvant CMF for 3, 6, 9 or 12 cycles (prolonged regimens) were not statistically significant.

Median survival from the start of chemotherapy for relapse was 22 months (25 months for 70 pts without tamoxifen bias). Survival from start of chemotherapy for relapse was significantly longer for patients with metastatic disease in soft tissue compared with those having bone or visceral involvement ($P < 0.0001$) (Figure 1). Patients with a therapy-free interval longer than 2 years had a longer survival from relapse compared with patients having shorter therapy-free intervals, but the difference was not statistically significant ($P = 0.07$) (Figure 2). By restricting the analysis to the patients treated with prolonged adjuvant therapy, the results were contradictory: for the 52 patients the differences in survival from the start of relapse therapy achieved statistical significance ($P = 0.01$) and were longer in patients with a longer therapy-free interval. This was not the case when considering the 35 patients without possible tamoxifen-induced response ($P = 0.51$) (Table 5).

Table 5. Overall survival from start of relapse therapy for patients treated with prolonged adjuvant therapy

	All patients				Patients without tamoxifen bias			
	Patients	Dead	5-Year survival % (se)	*P* value	Patients	Dead	5-Year survival % (se)	*P* value
All patients	52	42	21 (6)		35	25	26 (8)	
Dominant metastatic site								
soft tissue	30	20	33 (9)	< 0.0001	21	11	43 (12)	< 0.0001
bone	6	6	17 (15)		5	5	0 (0)	
viscera	16	16	0 (0)		9	9	0 (0)	
Therapy-free interval								
6–12 months	8	7	13 (12)	0.01	5	4	20 (18)	0.51
> 12 < 24 months	16	14	13 (8)		8	6	0 (0)	
> 24 months	28	21	29 (9)		22	15	28 (10)	

DISCUSSION

This study was conducted by treating patients upon relapse with the same chemotherapy regimen previously used in the adjuvant setting. The results of the study indicated that response rates were similar to those reported in the literature for treatment of advanced breast cancer with a CMF combination chemotherapy. In addition, the patterns of relapse and the number of metastatic sites were the most important factors predicting response to salvage treatment, while treatment-free interval (mostly longer than 6 months due to the study design) did not influence response rates. These results are in line with those of Valagussa and associates [5], but do not fully agree with the conclusion of a recent review on this topic by Rubens and co-workers [7] which claims that '...adjuvant systemic treatment compromises response of the disease to either endocrine therapy or chemotherapy after relapse'. It is important to note that this review did not account for the interval between completion of adjuvant treatment and time of systemic relapse and the timing of re-introduction of either cytotoxic or endocrine therapies. In addition, some of the conclusions relate to response to endocrine therapy in patients whose initial systemic adjuvant therapy was cytotoxic.

The patterns of relapse after adjuvant chemotherapy were the subject of a detailed investigation by the International Breast Cancer Study Group [15] and indeed the selection of patients to enter the current study significantly favoured inclusion of patients with soft tissue metastases.

The observation that commonly survival after relapse is shorter for patients who have had prior adjuvant systemic therapy than for patients who received no systemic therapy until first relapse was documented by several investigators and by our group. The population of patients was, in fact, not representative of the entire population of patients which experienced relapse. Thus, we are unable to draw conclusions about the magnitude of treatment effects upon relapse in terms of median duration of response.

The results of our study support the hypothesis suggesting the effectiveness of late re-introduction of adjuvant cytotoxic therapy (prior to evidence of systemic relapse), upon which several current trials are based. It is claimed that drug-sensitive cells, which are dormant during the initial treatment period, making them resistant to most cytotoxic agents, enter the cell cycle after a treatment-free interval becoming sensitive to the late re-introduced treatment. The fact that many patients relapse with tumours that, on cytotoxic rechallenge, are found to be responsive to the adjuvant treatment, indicates that the strategy of delayed administration of chemotherapy (or endocrine agents) may lead to improved outcome.

The most efficient adjuvant treatments reduce first relapse sites mainly in soft tissue, in the mastectomy scar, in axillary nodes and supraclavicular nodes. The observation that metastases in these sites are also the type of relapses most responsive to retreatment supports our hypothesis that available treatments might still have an additional effect. However, the magnitude of this effect is likely to be small. The avoidance of relapses in visceral sites and in the skeleton might require a significant qualitative and quantitative change in our treatment strategies [15].

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Acknowledgements—We thank the patients, physicians, nurses and data managers who participated in the trials. We also gratefully acknowledge the initial support provided by the Ludwig Institute for Cancer Research and the continuing support for central coordination, data management and statistics provided by The Swiss Cancer League, The Cancer League of Ticino, The Swedish Cancer League, The Australia–New Zealand Breast Cancer Trials Group (NH&MRC Grants: 880513, 890028, 910420, 920876), The Australian Cancer Society, The Frontier Science and Technology Research Foundation and The Swiss Group for Clinical Cancer Research (SAKK).