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Original Paper

Characterisation of Complete Responders to Combination Chemotherapy for Advanced Breast Cancer: A Retrospective EORTC Breast Group Study

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This retrospective study was undertaken to characterise the natural history of women achieving complete response (CR) following standard dose combination chemotherapy for metastatic breast cancer (MBC), and to analyse the significance of various patient, disease and treatment characteristics in determining survival and time to disease progression. 75 patients achieving a CR following standard dose combination chemotherapy or combined chemoendocrine therapy for MBC have been studied. At a median follow-up of 6 years, 28% of patients are still alive, with 18 of 21 patients showing no evidence of disease. 15 (20%) patients, with median follow-up of 61 months from start of chemotherapy, have never experienced relapse. Median overall survival is 32.5 months. Multivariate analysis for survival identified inclusion of anthracyclines and WHO performance status as significant predictors of good long-term outcome. Concomitant hormonotherapy almost reached statistical significance in our multivariate analysis. Neither dominant site of disease nor disease-free interval were significant determinants of complete remission. With conventional dose combination chemotherapy, approximately 20% of women with MBC who have achieved a clinical CR have been shown to be expected to remain alive and free of disease at 5 years. Inclusion of an anthracycline appears to be an important determinant of durability of CR and patient survival.

Key words: complete remission, breast cancer, chemotherapy, multivariate analysis, prognostic factors, anthracyclines

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INTRODUCTION

THE ACHIEVEMENT of a clinical complete remission (CR) is a prerequisite for cure in patients treated with systemic therapies for metastatic malignancies. Women who achieve CR following chemotherapy for metastatic breast cancer have been shown, in previous reports [1], to have better disease-free and overall survival than those not achieving CR.

In this study, we have attempted to characterise the natural history of women achieving CR following standard dose combination chemotherapy or combined chemoendocrine therapy for metastatic breast cancer. Women were treated in one of five EORTC (European Organization for Research and Treatment of Cancer) Breast Cancer Cooperative Group protocols [2–7]. These phase II and III protocols included both anthracycline containing and CMF-type regimens. We have analysed patient, disease and treatment characteristics to assess their relative importance as prognostic factors for survival and time to progression.

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PATIENTS AND METHODS

Between April 1981 and March 1992, 1045 patients with metastatic breast cancer were enrolled in one of five EORTC Breast Cancer Cooperative Group protocols for patients with no prior chemotherapy for advanced disease [2–7]. A short description of these five protocols is pre-

sented in the Appendix. Accrual details for these five protocols, the number of patients enrolled in each study, and the chemotherapy regimens utilised are summarised in Table 1.

For the current analysis of complete responders, 114 patients were identified by the EORTC Data Centre as being potentially eligible, based on the initial response assessment performed by the principal investigator at each individual centre, verified by the chairman of each individual trial, and usually confirmed by external review of each individual study. 103 patient records were reviewed for the current analysis by 1 of 3 external reviewers (authors ET, ISF, AM) who reviewed each case with the principal investigator and/or study chairman. 11 patient records were unavailable.

Of the 103 patients for whom a review was possible, 75 were confirmed to meet the criteria for complete response (CR) as defined below. The reasons for the non-inclusion of the remaining 28 patients were as follows:

(1) CR not achieved in bone (12 patients);
(2) CR not achieved at other disease sites (11 patients);
(3) Inadequate documentation of outcome in bone (2 patients);
(4) Patient ineligible because of prior chemotherapy for metastatic/locally advanced disease (2 patients); and
(5) CR duration <4 weeks (1 patient).

Of note, 3 patients who were considered ineligible for analyses of the individual trials because of prior adjuvant chemotherapy or advanced age, but who did achieve a CR, are included in the current study.

Definitions

(a) Complete response (CR) was defined as the disappearance of all clinical evidence of disease for a minimum period of 8 weeks (UICC criteria) [8]. In the case of bone metastases, the criteria for complete response included clear evidence of complete bone recalcification on X-ray, accompanied by either normalisation of a previously abnormal bone scan or attainment of a near normal architecture of the involved bone lesions on X-ray [9].

(b) Duration of CR (time to progression) was defined as the interval between date treatment started and date of documented progression. This definition is in agreement with EORTC Breast Cancer Cooperative Group guidelines [10], but differs from WHO criteria utilised by other authors [9, 11] (interval between documentation of CR and detection of recurrent disease).

(c) Survival was measured from initiation of chemotherapy to death or last follow-up.

Statistical analyses

Time to progression and duration of survival curves were estimated using the Kaplan–Meier technique [12]. Differences in time to progression and duration of survival were compared using a two-sided logrank test [13]. To adjust for any confounding variables and to assess the relative importance of the potential prognostic factors, Cox's proportional hazards regression model [14] was used.

The Software for the Management and Analysis of Randomized Trials (SMART) was used for data management and verification, and the Statistical Analysis Software (SAS*) was used for analysis of data.

RESULTS

75 patients met the criteria for complete response. Age varied between 28 and 71 years with a median of 52 years. 34 patients (45%) were ≤50 years of age and 24 patients (32%) were premenopausal. The majority of patients (52, 69%) had a WHO performance status of 0. Most (59%) patients entered the study at time of first relapse, but 15% entered at the time of initial diagnosis of breast cancer, and 21% entered at the time of a second or later relapse.

Initial stage at diagnosis for patients was as follows: Stage I (12% patients), Stage II (45%), Stage III (6%), Stage IV (20%), unknown (17%). In the majority of cases, histological grade at times of diagnosis was unavailable. 31% of patients had tumours that expressed oestrogen receptors at time of diagnosis, 32% were receptor negative and in 37% the oestrogen receptor status was unknown.

Prior to randomisation in 1 of the 5 metastatic disease trials, 69% of patients had undergone mastectomy, 17% tumourectomy and 13% biopsy only. 23% of patients had received radiotherapy for locally recurrent or metastatic disease and 17% had received hormonal therapy for metastases. Only 9 and 8% of patients had received prior adjuvant chemo- or hormonal therapies, respectively. Among the 7 patients who received adjuvant chemotherapy prior to randomisation, the number of cycles varied between 2 and 12, with a median of 6 cycles.

Metastatic disease characteristics at entry are presented in Table 2. The disease-free interval (DFI) before randomisation varied between 0 and 126 months with a median of 17 months. 34 patients (45%) had visceral metastases. The proportion of patients with specific sites of metastatic involvement are listed in Table 2. In 43% of patients, soft tissue was the only site of metastases. Only 3 patients had bone metastases as the sole site of disease. In only 13% of patients was the oestrogen receptor status of metastatic disease determined.

Chemotherapy characteristics are shown in Table 3. 41 patients (55%) received an anthracycline as a component of their chemotherapy regimen, 39 received doxorubicin and 2 received mitoxantrone.

16 patients received more than three different cytotoxic agents in their original regimen as part of a phase III trial of alternating non-crossresistant regimens (protocol 10832). Twenty per cent of patients received oestrogenic recruitment prior to chemotherapy (protocols 10807, 10835). Forty-eight per cent of patients received concomitant hormones: aminoglutethimide and hydrocortisone ± oophorectomy in protocols 10807 and 10835 (25 patients), tamoxifen for postmenopausal patients in protocol 10832 (11 patients).

The median total number of chemotherapy cycles received was 15 (range 2–31). The median number of cycles to achieve CR was 6 (range 1–24). Patients received a median of 6 'consolidation' cycles following documentation of CR (range 0–29). The reasons for chemotherapy discontinuation are listed in Table 3. In the majority, treatment was discontinued because of excessive toxicity, patient refusal to continue or the end of protocol treatment. In only 21 patients (28%) was treatment actually stopped because of

Table 1. Trials in which patients were enrolled

Trial [reference]	Date activation	Date closed	Total accrual	CRs confirmed and included in this analysis	Chemotherapy regimen		Duration chemotherapy	Hormonal therapy
10807 [2,3]	25.04.81	08.07.83	57	7	FAC:	F = 500 mg/m^2 i.v. dl A = 50 mg/m^2 i.v. dl C = 500 mg/m^2 i.v. dl q 21 days	Until PD (switch to CMF when A > 550 mg/m^2) or 2 years total.	Oophorectomy* followed by medical adrenalectomy; all patients receive Erc.
10835 [4]	15.09.83	24.07.87	157	18	Idem		Idem	Idem; randomisation Erc.
10808 [5]	05.06.81	16.05.84	233	8	'Classical' CMF: 'i.v.' CMF:	C = 100 mg/m^2 po dl, 14 M = 40 mg/^{2} i.v. dl, 8 F = 600 mg/m^2 i.v. dl, 8 q 28 days C = 600 mg/m^2 i.v. dl M = 40 mg/m^2 i.v. dl F = 600 mg/m^2 i.v. dl q 21 days	Until PD	No
10832 [6]	27.11.83	23.03.89	135	26	'Classical' CMF as above AMi: DDP/Vd:	A = 40 mg/m^2 i.v. dl Mi = 100 mg/m^2 i.v. dl, 10 DDP = 100 mg/m^2 i.v. dl Vd = 3 mg/m^2 i.v. dl, 8	Until PD	Tamoxifen for postmenopausal.
10852 [7]	09.12.85	25.03.92	463	16	'Classical' CMF as above		Randomisation after six cycles to continue or stop chemotherapy. If continue until PD.	No
Total	—	—	1045	75	—		—	—

A, doxorubicin; C, cyclophosphamide; DDP, cisplatin; F, 5-fluorouracil; M, methotrexate; Mi, mitolactol; Vd, vindesine; Erc, oestrogenic recruitment; PD, progressive disease; i.v., intravenous; d, day; q, every; p.o., oral; Idem, as shown above.

* In premenopausal patients.

Table 2. Characteristics of metastatic disease at entry to the original trial

	Number (%)
Disease-free interval (months)	
0	14 (19)
1–6	8 (11)
7–12	7 (9)
13–24	21 (28)
25–36	9 (12)
>36	16 (21)
Dominant site of disease	
Soft tissue	32 (43)
Bone	8 (11)
Visceral	34 (45)
Other	1 (1)
Liver involvement	
No	58 (77)
Only metastatic site	3 (4)
With other metastases	3 (4)
Unknown	11 (15)
Lung parenchymal involvement	
No	51 (68)
Multiple nodules	20 (27)
Other	3 (4)
Unknown	1 (1)
Bone involvement	
No	61 (81)
Only metastatic site	3 (4)
With other metastases	9 (12)
Unknown	2 (3)
Pleural involvement	
No	61 (81)
With other metastases	14 (19)
Soft tissue/nodal involvement	
No	23 (31)
Only metastatic site	32 (43)
With other metastases	20 (27)
Oestrogen receptor status	
0	1 (1)
1–29	2 (3)
30–100	6 (8)
>100	1 (1)
Unknown	65 (87)

Table 3. Chemotherapy received

Chemotherapy	Number (%)
Anthracyclines	
No	34 (45)
Yes	41 (55)
Number of drugs	
≤ 3	59 (79)
>3	16 (21)
Oestrogenic recruitment	
No	60 (80)
Yes	15 (20)
Concomitant hormonotherapy	
No	39 (52)
Yes	36 (48)
Concomitant radiotherapy	
No	74 (99)
Yes	1 (1)
Number of cycles to achieve CR	
≤ 6	44 (59)
>6	31 (41)
Number of cycles to consolidation	
≤ 6	38 (51)
>6	37 (49)
Total number of cycles	
≤ 15	40 (53)
>15	35 (47)
Reason for chemotherapy discontinuation	
Death	1 (1)
Treatment refused	21 (28)
Excessive toxicity	9 (12)
Progression-recurrence	21 (28)
End of protocol treatment	20 (27)
Other	3 (4)
Status at time consolidation discontinued	
NED	52 (69)
Relapse progression	23 (31)

NED, no evidence of disease.

disease progression or recurrence. There were 3 treatment related deaths: 1 patient died with refractory congestive heart failure after receiving a total cumulative dose of 535 mg/m^2 of doxorubicin, and 2 patients died of septic complications.

When doxorubicin was administered (39 patients), the total dose in mg/m^2 ranged between 76 and 650 mg/m^2 with a median of 490 mg/m^2. There was only 1 other patient in this series of complete responders who developed symptomatic cardiomyopathy related to anthracycline administration. This second patient was initially treated with 440 mg/m^2 of doxorubicin and subsequently developed congestive heart failure on retreatment with seven cycles of mitoxantrone 4 years later at time of relapse. She is currently alive with no evidence of disease.

At the present time, 60 (80%) patients have relapsed after achieving CR. The median time to progression based on all patients was 19.5 months (Figure 1). Sites of first relapse are as follows: in 62% of patients, relapse occurred at the initial dominant site only. In 22%, relapse was at a site not

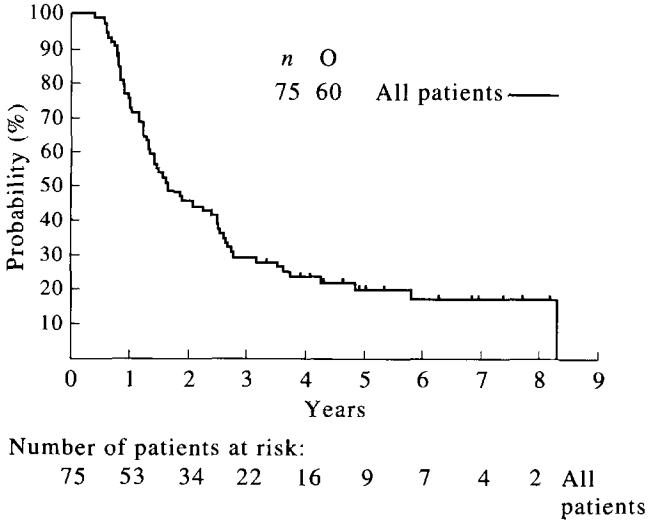

Figure 1. Time to progression. *n*, total number of patients; O, total relapses.

initially involved. In 17%, relapse occurred at the initially involved site and new sites. The total number of different sites involved at relapse from CR are as follows: one site (65%), two sites (22%), three or more sites (11%), unknown (2%). Relapse involved the lung in 22% of patients, liver (10%), bone (22%), pleura (23%), and soft tissue in 53% of patients.

8 patients relapsed in the central nervous system at time of first relapse. This represents 13% of first relapses. A total of 15 patients (25% of patients with relapse) had CNS involvement at some time during their clinical course. Table 4 provides information concerning CNS involvement. In 67% of cases, CNS relapse was associated with systemic failure. Treatment varied, with 11 patients receiving cranial irradiation. Only 3 patients had short-lived responses to treatment and in most cases CNS involvement contributed directly to death.

Table 5 presents details of treatment for all 60 relapsed patients. 24 patients received further chemotherapy and 4 (17%) responded. Response lasted for 5 months in 2 patients and for 9 months in the other 2. 3 other patients responded to subsequent hormonal therapy. Duration of these responses was unavailable. Of those responders, none had further CR or PR with subsequent chemo- or hormonal therapies.

Table 4. CNS involvement

	Number (%)
CNS involvement at any relapse (60 patients)	
No	40 (67)
Single cranial	3 (5)
Multiple cranial	8 (13)
Leptomeningeal	3 (5)
Other	1 (2)
Unknown	5 (8)
Which relapse (if CNS involvement, 15 patients)	
First	7 (47)
Second	4 (27)
Third	1 (7)
Fourth	2 (13)
Unknown	1 (7)
Association with systemic failure (15 patients)	
Isolated CNS involvement	4 (27)
Associated with systemic failure	10 (67)
Unknown	1 (7)
Treatment (15 patients)	
No treatment	2 (13)
Cranial irradiation	7 (47)
Intrathecal therapy	1 (7)
Combination	4 (27)
Unknown	1 (7)
Best response	
PR*	3 (20)
PD	8 (53)
Not evaluable	1 (7)
Unknown	3 (20)
Contribution to death	
No	1 (7)
Yes	11 (73)
Unknown	3 (20)

* Responses lasted for 1 month, 7 months, and for an unknown period
PR, partial response; PD, progressive disease.

Table 5. Treatment at first relapse

	Number (%)
Type of systemic treatment at time of first relapse	
None	17 (28)
Chemotherapy	20 (33)
Hormonotherapy	17 (28)
Chemotherapy + hormonotherapy	4 (7)
Other (intrathecal)	1 (2)
Unknown	1 (2)
Number of cycles of chemotherapy (24 patients)	
1–3	12 (50)
4–6	7 (29)
7–9	3 (13)
>9	2 (8)
Type of local treatment at time of first relapse	
None	38 (63)
Radiation	20 (33)
Surgery	1 (2)
Unknown	1 (2)
Response to systemic chemotherapy (24 patients)	
CR	1 (4)
PR	3 (13)
NC	6 (25)
PD	9 (38)
Not evaluable	4 (17)
Unknown	1 (4)
Response to systemic hormonotherapy (21 patients)	
CR	2 (10)
PR	1 (5)
NC	4 (19)
PD	13 (62)
Unknown	1 (5)

Survival data and status of patients who are alive when last traced, as well as causes of death are presented in Table 6. The median duration of survival is 32.5 months (Figure 2). 21 (28%) patients remain alive, 18 with no evidence of disease. 54 patients (72%) have died, 91% with progressive disease.

Univariate and multivariate analysis of prognostic factors for survival and time to progression

The relative importance of various patient, disease and treatment related variables on duration of survival and time to progression was assessed using the Cox proportional hazards regression model [14].

Twenty-two variables were considered in univariate analyses for survival and time to progression: age ($\leqslant 50$ versus >50 years), menopausal status, performance status (PS), initial T category, initial N category, initial stage, initial tumour grade, initial oestrogen receptor (ER) status, prior chemotherapy, prior hormonotherapy, DFI, dominant site, liver involvement, lung involvement, bone involvement, soft tissue as only site of involvement, inclusion of anthracycline, oestrogenic recruitment, number of drugs, concomitant hormonotherapy, number of cycles to achieve CR ($\leqslant 6$ versus >6), and time of entry on trial (initial diagnosis versus first relapse versus second or later relapse).

Nine variables were chosen for multivariate analysis based on the results of the univariate analysis. A backward (step down) procedure was used at the 5% level of significance for variable selection. The nine variables considered were: age, menopausal status, WHO performance status, disease-

Table 6. Survival status

	Number (%)
Still alive when last traced	21 (28)
Last unknown status	
NED, no treatment	7 (33)
NED, hormonotherapy	9 (43)
NED, no information concerning the treatment	2 (10)
Relapse, treatment	2 (10)
Relapse, no information concerning the treatment	1 (5)
Number of deaths	54 (72)
Cause of death	
Malignant disease	49 (91)
Toxicity	1 (2)
Infection	2 (4)
Cardiovascular	1 (2)
Unknown	1 (2)

NED, no evidence of disease.

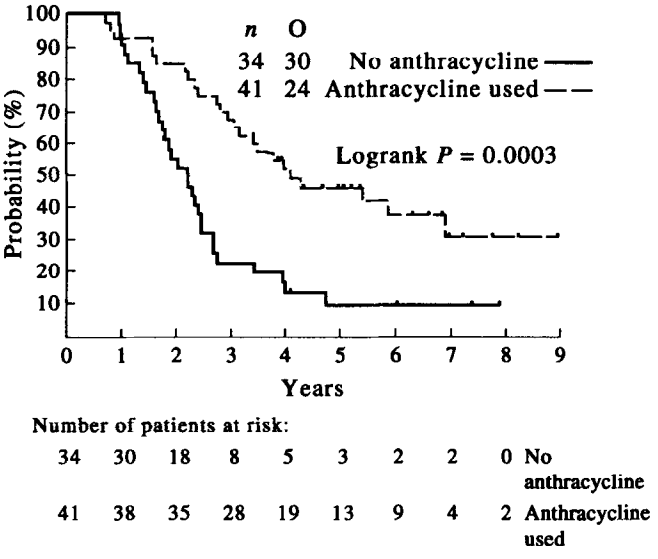

Figure 3. The effect of inclusion of an anthracycline in treatment for metastatic breast cancer on survival. *n*, total number of patients; O, number of deaths.

free interval, chemotherapy including anthracyclines, oestrogen recruitment, number of drugs used, concomitant hormonotherapy, and number of cycles to achieve complete response. The number of 'consolidation' cycles of chemotherapy received following achievement of CR was not included in this analysis, as this was measured after achieving CR, possibly biasing the results as patients who die early can obviously have only a small number of consolidation cycles.

The following variables were significant in the univariate analysis for survival: WHO performance status (0 versus >0), chemotherapy including anthracyclines (yes versus no), concomitant hormonotherapy (yes versus no), and number of cycles to achieve complete response ($\leqslant 6$ versus >6).

The multivariate model for survival selected the following prognostic factors at the 5% level of significance: inclusion of anthracyclines (Table 7) and WHO performance status. With these two variables already in the model, concomitant hormonotherapy was of borderline significance ($P = 0.068$).

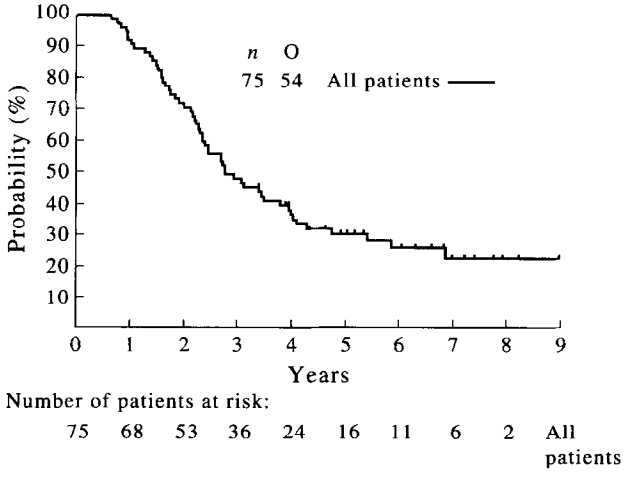

Figure 2. Duration of survival. *n*, total number of patients; O, number of deaths.

The following variables were significant in the univariate analysis for time to progression: menopausal status, chemotherapy including anthracyclines, oestrogen recruitment, concomitant hormonotherapy, and number of cycles to achieve complete response. The performance status had a borderline significance ($P = 0.061$).

The multivariate model for time to progression selected only the inclusion of anthracyclines at the 5% level of significance.

Tables 7 and 8 summarise the univariate results of the prognostic factor analysis for survival and time to progression, respectively. The multivariate results are presented in Table 9.

Long-term relapse-free survivors

15 (20%) patients, with median follow-up of 61 months from start of chemotherapy, have never experienced relapse. Their characteristics are displayed in Table 10. 1 of these patients has died with refractory congestive heart failure related to chemotherapy. Most (13/15) of these patients received anthracycline-based chemotherapy. 11 also received some form of hormonal therapy: tamoxifen in 2 patients, aminoglutethimide and hydrocortisone in 4 patients, and oophorectomy followed by chemical adrenalectomy in 5 patients. 9 of these patients had visceral metastases at study entry (6 lung, 3 liver). Initial oestrogen receptor status is listed in Table 10.

DISCUSSION

In this retrospective study, we have attempted to characterise women with metastatic breast cancer who achieve a CR to conventional dose combination chemotherapy, and to describe their natural history. We have also performed a multivariate analysis of patient, tumour and treatment variables to identify factors predictive of long-term overall and disease-free survival.

Table 7. Duration of survival according to possible prognostic factors

Variable	Number of patients	Number of deaths	Median duration of survival (months)	Hazard ratio	Logrank *P*
Patient and tumour characteristics at entry					
Age (years)					
⩽50*	34	22	39.8		
>50	41	32	30.2	1.46	0.167
Menopausal status					
Premenopausal*	24	15	47.9		
Postmenopausal	51	39	27.8	1.7	0.076
Performance status					
WHO = 0*	52	35	40.8		
WHO ⩾ 1	23	19	22.5	2.20	0.005
Disease-free interval					
>6 months	53	39	31.7		
⩽6 months*	22	15	40.9	1.27	0.425
Disease-free interval					
>12 months	46	34	31.8		
⩽12 months*	29	20	38.3	1.25	0.420
Dominant site					
Visceral*	31	22	35.9		
No	44	32	32.4	1.03	0.919
Chemotherapy characteristics prior to CR					
Anthracyclines					
No	34	30	25.6		
Yes*	41	24	48.6	2.56	0.0003
Oestrogenic recruitment					
No	60	46	31.6		
Yes*	15	8	60.7	1.89	0.095
Number of drugs					
⩽3	59	44	28.9		
>3*	16	10	43.9	1.54	0.207
Concomitant hormonotherapy					
No	39	33	26.9		
Yes*	36	21	55.0	2.44	0.0007
Number of cycles before CR					
⩽6	44	35	26.7		
>6*	31	19	47.2	1.85	0.027

* Reference category.

Six other groups [1, 9, 11, 15–17] have reported analyses of complete responders in the same clinical situation. The number of patients analysed in these reports and their median survivals are presented in Table 11. As in our series, chemotherapy regimens varied and did not always include an anthracycline. Variable proportions of patients received concomitant or sequential hormonal therapies. Treatment was usually continued until relapse or for a total of 2 years.

The largest series is reported by Hortobagyi and associates, with 221 complete responders followed for at least 6 years [17]. All patients received doxorubicin-based chemotherapy. The median time to progression (24 months) and overall survival (37 months) reported in their series are remarkably similar to our results (19.5 and 32.5 months, respectively).

Our report confirms several observations made in previous publications. In all series, patients achieving a complete response represented a very small minority of all patients treated, considerably lower than the usually quoted 20% clinical CR rate achieved with chemotherapy [18]. Uniformly, the vast majority of complete responders relapse (range from 61 to 90% in the published series). The majority of patients relapse at sites of previous involvement (63 and 76% reported by Fischer and associates [11] and Legha and associates [9]; 62% in our own series).

As described by Fischer and colleagues [11], the presence of visceral disease does not preclude the achievement of a durable complete remission. In our own series, 9 of 15 long-term survivors who never experienced relapse presented with visceral involvement (Table 10). Relapse in the central nervous system (CNS) is relatively common, documented in 15 of our 60 patients with relapse (25%). This proportion is in agreement with the frequencies reported by Fischer and colleagues [11], Decker and colleagues [15] and Legha and colleagues [9]: 7, 14 and 24%, respectively.

Our results are in disagreement with previous publications in two areas. We were unable to confirm the findings of several other groups who reported dominant site of disease [1, 16], and disease-free interval [1, 15] to be important determinants of outcome in complete responders. Secondly, our data do not support the observation made by Feldman and colleagues [19] that most long-term survivors achieve CR rapidly (within 3 months of start of treatment). In our multivariate analysis, the number of cycles required to achieve CR was not an important determinant of either overall survival or time to progression in all 75 patients, and among

Table 8. Time to progression according to possible prognostic factors

Variable	Number of patients	Number of patients having recurrence	Median time to progression (months)	Hazard ratio	Logrank *P*
Patient and tumour characteristics at entry					
Age (years)					
⩽50*	34	26	29.3		
>50	41	34	18.4	1.39	0.195
Menopausal status					
Premenopausal*	24	17	32.9	1.91	0.018
Postmenopausal	51	43	15.6		
Performance status					
WHO = 0*	52	40	28.3		
WHO ⩾ 1	23	20	11.1	1.60	0.061
Disease-free interval					
>6 months	53	44	18.4		
⩽6 months*	22	16	19.6	1.30	0.371
Disease-free interval					
>12 months	46	38	17.8		
⩽12 months*	29	22	20.9	1.41	0.194
Dominant site					
Visceral*	31	23	28.3		
No	44	37	17.2	1.26	0.379
Chemotherapy characteristics prior to CR					
Anthracyclines					
No	34	32	11.3		
Yes*	41	28	31.8	3.22	< 0.0001
Oestrogenic recruitment					
No	60	50	17.2		
Yes*	15	10	43.1	1.92	0.046
Number of drugs					
⩽3	59	48	16.5		
>3*	16	12	30.2	1.45	0.239
Concomitant hormonotherapy					
No	39	34	14.3		
Yes*	36	26	31.5	2.38	0.0004
Number of cycles before CR					
⩽6	44	37	14.1		
>6*	31	23	29.4	2.00	0.008

* Reference category.

our never relapsed patients, the median number of cycles prior to documentation of CR was 7 with a range of 1–19. A possible explanation for the discrepancy in results between Feldman's series and our own, is that chemotherapy alone was given to patients in Feldman's series, whereas most of the long-term survivors of our present series were treated with hormonochemotherapy. Such a combination might be related to our results and might affect the pattern of achievement of complete response.

Our report is the first analysis of CRs to analyse characteristics of treatment received and to identify the inclusion of an anthracycline as an important determinant of durability of complete response and patient survival.

In addition, with a relatively long follow-up of patients (median 71 months, maximum 8.9 years), we have been able to estimate the proportion of complete responders who remain disease-free at 5 and 8 years of follow-up (20 and 18%, respectively). These statistics have only been reported by one other group. In the MD Anderson experience, 12.5 and 9% of CRs were disease-free at 5 and 10 years, respectively [17]. Such data are essential, in the absence of completed randomised controlled trials, to place into proper perspective the encouraging reports of durable complete remissions in women with metastatic breast cancer treated with high-dose chemotherapy and autologous bone marrow transplantation [20, 21]. The use of high-dose chemotherapy regimens has been shown to result in the achievement of higher CR rates (weighted average of 36% in a recent review [22]) than reported with conventional dose combination chemotherapy programmes in metastatic disease (0 to 36%, with a disappointing weighted average of 18% [22]). In the absence of data documenting improvement in overall survival with such approaches, attention has turned to the durability of CRs achieved, with Peters and coworkers from Duke University reporting a projected 6-year disease-free survival of 14% in a small number of previously untreated patients presenting with metastatic breast cancer [20]. Our data and that of Hortobagyi and colleagues suggest that selected patients may have a similar outcome with less dose-intensive treatment.

Only Decker and colleagues [15] have previously reported on the results of salvage systemic therapy at the time of relapse from CR. In their series, 10 of 25 patients responded, with 7 and 3 patients achieving PR and CR re-

Table 9. Results of the Cox proportional hazards regression model

	Conditional relative risk	(95% CI)	*P*
Duration of survival			
Anthracyclines included			
No	1		
Yes*	2.56	(0.22–0.67)	0.0008
WHO performance status			
0*	1		
1–2	2.07	(1.17–3.66)	0.012
Time to progression			
Anthracyclines included			
No	1		
Yes*	3.57	(0.16–0.47)	0.0001

* Reference category.

spectively. Our own results are less favourable: second-line chemo- or hormonal therapy were associated with only 17 and 15% response rates, and no patient responding to second-line therapy responded to subsequent systemic therapeutic manoeuvres. These lower response rates may reflect the difficulty in evaluating response in our patients of which 45% had either bone or pleural metastases, or may relate to the fact that these patients received a long duration of continuous chemotherapy, perhaps resulting in high rates of induction of chemoresistance.

Finally, although concomitant hormonotherapy did not reach a level of statistical significance in the multivariate analysis of survival and time to progression, our observation that 11 of 15 patients without relapse had also received hormonotherapy supports Pedrazzini's provocative hypothesis that endocrine therapy is crucial for achievement of a durable CR [16].

We were unable to reach any meaningful conclusion regarding the impact of consolidation chemotherapy in patients achieving CR as this variable was not analysed. The patients treated on these five EORTC protocols, in general, received longer duration of continuous chemotherapy than is usually given in routine clinical practice today. It is interesting to note that patients never experiencing relapse received, on average, 14 cycles of chemotherapy following CR (range 1–20).

Three factors may make generalisations from this analysis difficult to apply to patients in the current era. Firstly, at the time patients were entered into the earlier trials of this analysis, data concerning hormone receptor levels and histological or nuclear grade, both important predictors of treatment response and prognosis, were not available on a routine basis. Having such information available may have influenced the choice of therapies offered to patients at the time of development of metastases. Secondly, in the current report, only 9 and 8% of patients received adjuvant chemo- or hormonal therapies, respectively. Currently, patients are much more likely to receive adjuvant systemic therapies, which may prejudice their chance to respond to subsequent regimens [23–25] and could possibly alter the character or

Table 10. Characteristics of patients never experiencing relapse (n = 15)

Menopausal status	Pre	7/15		
	Post	8/15		
PS	WHO = 0	12/15		
	WHO = 1	3/15		
Initial ER status (fmol/l)	0	4/15		
	1–100	6/15		
	>100	1/15		
	Unknown	4/15		
Prior adjuvant chemotherapy	None	15/15		
Prior hormonal therapy	None	14/15		
	For locally advanced disease	1/15		
DFI	Median 13 month (range 0–56 months)			
Dominant site	Visceral	9/15*		
	Bone	1/15		
	Soft tissue	5/15		
Duration CR (from start chemotherapy)	Median 61 months (range 9†–96 months)			
Number of cycles to achieve CR	Median 7 (range 1–19)			
Number cycles 'consolidation'	Median 14 (range 1–20)			
Inclusion anthracycline	Yes	13/15		
	No	2/15		
Number drugs	⩽3	11/15		
	>3	4/15		
Concomitant hormones	No	4/15		
	Yes	11/15:	Tamoxifen	2/15
			AG + HC	4/15
			Oophorectomy + AG + HC	5/15

AG, aminoglutethimide; HC, hydrocortisone.

* 6 lung, 3 liver. † Patient with shortest duration CR died of anthracycline related cardiomyopathy.

Table 11. Other reports of complete responders to conventional chemotherapy for metastatic breast cancer

[Ref.]	Total number of patients	Number of patients with CR	Follow-up	Median duration CR*	Median TTP†	Median survival‡	Recurrences	Time to recurrence	Median time to CR	Prognostic factors	Chemotherapy regimens	Concomitant	Duration chemotherapy
[9]	619	116 (18%)	>24 mos	17 mos	—	N/A	81/116 (70%)	3–44 mos	5 mos (r1-23)	bulk disease (>3 sites), oophorectomy + chemo	FAC followed by CMF	Oophorectomy in 23	Usually 2 years post CR
[16]	422	60 (14%)	>5 y	—	27.5 mos	52.5 mos	39/53 (73%)	N/A	N/A	Dominant site, number sites	3 regimens (± A)	Concurrent or sequential, oophorectomy or tamoxifen	2 years post CR
[15]	438	49 (11%)	N/A	—	13.5–19 mos+	21–28 mos+	42/49 (86%)	N/A	N/A	DFI>5 y, within 5 y menopause	Variable (± A)	No	2 years post CR
[11]	647	27 (4%)	2–8 y	27.5 mos	—	N/A	19/27 (70%)	1–51 mos	8.1 mos (r1-19.5)	< 2 sites (NSS)	Variable (± A)	No	Until PD
[1]	N/A	28	N/A	26 mos	—	45.5 mos	17/28 (61%)	N/A	N/A	DFI<2 y, visceral involvement	Doxorubicin-based	N/A	N/A
[17]	1424	221 (15%)	6–13.5 y	—	24 mos	37 mos	198/221 (90%)	N/A	N/A	N/A	A, C ± F, Vcr, M	No	1 year post CR or 2 years total
Current report (Tomiak)	1045	75 (7%)	Median 71 mos (max 8.9 y)	—	19.5 mos	32.5 mos	60/75 (80%)	N/A	6 cycles (r1-24)	Anthracycline use, PS	See Table 1	See Table 1	See Table 1

* From documentation CR to time recurrence. †From day 1 of study (or start chemotherapy). ‡From day 1 of study (or start chemotherapy).
TTP, time to progression; N/A, not available; r, range; NSS, not statistically significant; A, doxorubicin; C, cyclophosphamide; Vcr, vincristine; M, methotrexate; PD, progression; F, 5-Fluorouracil; CR, complete response; DFI, disease-free interval.

duration of response. Thirdly, patients enrolled into these five multicentric studies may not be representative of the majority of women with metastatic breast cancer who are treated outside the context of clinical trials. Patients in clinical trials often have better reported outcomes than those treated outside of a clinical trial setting as a result of selection criteria and restrictive entry criteria.

In conclusion, we have reported that patients achieving a clinical complete remission following standard dose combination chemotherapy have a median survival of 32.5 months and that median follow-up of 6 years, 28% of patients are still alive, with 18 of 21 patients showing no evidence of disease. Amongst several patient, tumour, and treatment variables, the inclusion of an anthracycline and initial performance status emerge as the most important predictive factors for time to progression and survival. Concomitant hormonotherapy almost reached statistical significance in our multivariate analysis.

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APPENDIX

(1) Protocol 10807

A phase II trial assessing cyclic combination chemotherapy with oestrogenic recruitment, in which patients were treated with chemical adrenalectomy (aminoglutethimide plus hydrocortisone) and oestrogenic recruitment prior to FAC chemotherapy. Premenopausal patients underwent oophorectomy before chemical adrenalectomy [2, 3].

(2) Protocol 10835

A phase III randomised double-blind trial evaluating the efficacy of oestrogenic recruitment in patients treated with chemical adrenalectomy plus FAC, as described above [4].

(3) Protocol 10808

A phase III randomised trial comparing 'classical' CMF versus a 3 weekly intravenous CMF schedule in postmenopausal patients [5].

(4) Protocol 10832

A phase III randomised trial comparing alternating and sequential administration of three non-crossresistant chemotherapy regimens [6].

(5) Protocol 10852

A phase III randomised trial comparing 'short' versus 'long' term CMF in postmenopausal patients [7].