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Specialist Interest Articles

Long-term Survival of Patients Treated with Combination Chemotherapy for Metastatic Breast Cancer

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Long-term survival of patients with metastatic breast cancer treated on two prospective stratified randomised trials has been analysed. Patients on study B122 received either cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin and 5-fluorouracil (CAF). On study B141 patients received CAF or mitolactol (dibromodulcitol), doxorubicin and vincristine alternating after every three cycles with three cycles of CMF (DAV/CMF). Long-term follow-up of 172 patients showed no significant survival difference (in multivariate regression models) for treatment with either CMF vs. CAF or CAF vs. DAV/CMF. The difference in median survival times between CMF and CAF showed a trend in favour of CAF. Advances in the management of metastatic breast cancer in postmenopausal women obtained by doxorubicin regimens have had a small but measurable impact on survival, but known patient discriminants were not overridden by the treatment regimens investigated in these studies.
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INTRODUCTION

IT IS generally accepted that the use of combination chemotherapy has resulted in improved response rates for patients with metastatic breast cancer. However, the relative survival advantage for patients treated with different cytostatic combinations is less clear. Multivariate regression analyses emphasise the continued importance of patient discriminants. Until recently few prospectively stratified randomised clinical trials were undertaken. In view of continued uncertainty of survival advantages with different cytostatic combinations it is important to analyse long-term follow-up results in randomised stratified trials. We have data on such trials started 18 years ago.

The present report deals with two studies started in 1972 and 1974 by the Breast Cancer Group of the NCI at Bethesda in cooperation with the University of Pretoria. Long-term survival data for the patients entered onto these prospectively stratified randomised studies are presented. The number of patients in the long-term follow-up analysis is the same as the number of eligible patients reported in the initial publications. Ineligible patients were censored and have been excluded from subsequent analysis. The results of the first study, B122, in 1978 showed a response rate of 62% with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and a response rate of 82% with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) [1].

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The projected median survival time reported for patients treated with CMF was 17 months while for patients treated with CAF this was 27.2 months. This difference was not statistically significant. The results of the second study, B141, in 1979 showed a response rate of 67.4% on CAF and of 77.1% on mitolactol (dibromodulcitol), doxorubicin and vincristine for three cycles sequential alternating with three cycles of CMF (DAV/CMF) [2]. These response rates were not significantly different, and there was no survival difference for the two treatment arms, but only 8 of the 100 patients on this study had died at that time.

MATERIALS AND METHODS

B122

Stratification and randomisation for the US hospitals were done centrally at the NCI using the method of Pocock and Simon [3]. South African patients were randomised using sealed envelopes. The envelopes were supplied for each stratification by the NCI. 92 patients were entered on study. 14 were excluded from analysis as they were ineligible [1]. Data from 78 patients entered on study B122 were analysed. All patients had histologically proven breast cancer with evidence of progressive metastatic disease. No patient had received prior chemotherapy. Eligibility criteria have been described [1].

Pretreatment characteristics and baseline variables of the patients were not statistically significantly different between the two treatment arms. Because of the prerandomisation stratification, the two arms of the protocol were completely comparable with regard to dominant disease site. Patients were stratified within the randomisation according to criteria expected to affect response to therapy including menstrual status, disease-free

Table 1. Pretreatment characteristics and stratification of patients: a comparison of baseline values between B122 and B141

	Protocol		
	B122	B141	*P*
Age (yr)*			
<50	34 (43%)	28 (29%)	
≥50	44 (56%)	66 (70%)	0.061
Disease-free interval (yr)			
<1	39 (50%)	29 (30%)	
1–3	23 (29%)	42 (44%)	
≥3	15 (19%)	23 (24%)	
Unknown	1 (1%)		0.029
Menopausal status*			
Unknown		1 (1%)	
Premenopausal	6 (7%)	3 (3%)	
Postmenopausal	72 (92%)	90 (95%)	0.282
Prior hormonal response			
Yes	14 (17%)	4 (4%)	
No	22 (28%)	20 (21%)	
Unknown	42 (53%)	70 (74%)	0.004
Performance status (Karnofsky)			
<80	22 (28%)	20 (21%)	
80–90	27 (34%)	38 (40%)	
≥90	29 (37%)	28 (29%)	
Unknown		8 (8%)	0.452
Dominant disease			
Visceral	46 (58%)	49 (52%)	
Osseous	21 (26%)	34 (36%)	
Soft tissue	11 (14%)	11 (11%)	0.429
No. of sites			
1	18 (23%)	39 (41%)	
2	27 (34%)	31 (32%)	
3	33 (42%)	24 (25%)	0.018
Dire disease			
No	44 (56%)	48 (51%)	
Yes	34 (43%)	46 (48%)	0.484
Postmenopausal interval (yr)			
≤1	31 (39%)	21 (22%)	
1–5	12 (15%)	23 (24%)	
≥5	29 (37%)	48 (51%)	
Unknown	6 (7%)	2 (2%)	0.021
Time from recurrence to on study (mos)			
<6	60 (76%)	72 (76%)	
6–12	7 (8%)	7 (7%)	
≥12	10 (12%)	15 (15%)	
Unknown	1 (1%)		0.817
Country			
USA	62 (79%)	43 (45%)	
South Africa	16 (20%)	51 (54%)	0.000

*At on study.

interval, number of disease sites and dominant disease site (Table 1).

Both regimens were given at 4 week cycles: the CMF programme consisted of cyclophosphamide 100 mg/m^2 given orally as a single daily dose on days 1–14, 5-fluorouracil 600 mg/m^2 given intravenously on days 1 and 8 of each cycle and methotrexate 40 mg/m^2 intravenously on day 1 and 8 of each cycle. The CAF programme included cyclosphosphamide 100 mg/m^2 orally on days 1–4, 5-fluorouracil 500 mg/m^2 intravenously on days 1 and 8 and doxorubicin 30 mg/m^2 intravenously on days 1 and 8 of each cycle. Both regimens were continued till evidence of progression of disease, but after a total dose of 450 mg/m^2 doxorubicin was achieved, methotrexate 40 mg/m^2 intravenously on days 1 and 8 of each cycle was substituted and the 5-fluorouracil dose increased to 600 mg/m^2. This was done in order to avoid cardiotoxicity.

B141

100 patients were entered on study of whom 6 were ineligible. Data of 94 patients with progressive metastatic breast carcinoma entered on study B141 were analysed. The patients had measurable and/or evaluable disease as defined by the guidelines of the Breast Cancer Task Force Combination Chemotherapy Trials Working Group [4]. The other eligibility criteria have been reported [2].

Patients were randomly allocated by an adaptive stratification technique [3] to receive one of two regimens: (1) 28-day cycles of cyclophosphamide 100 mg/m^2 orally days 1–4, doxorubicin 30 mg/m^2 intravenously days 1 and 8 and 5-flourouracil 500 mg/m^2 intravenously days 1 and 8 (CAF); or (2) 28-day cycles of mitolactol 135 mg/m^2 orally days 1–10, doxorubicin 45 mg/m^2 intravenously day 1 and vincristine 1.2 mg/m^2 (maximum dose 2.0 mg) intravenously days 1 and 8, alternating after each third cycle with three 28-day cycles of cyclophosphamide 100 mg/m^2 orally days 1–14, methotrexate 40 mg/m^2 intravenously days 1 and 8 and 5-flourouracil 600 mg/m^2 intravenously days 1 and 8 (DAV/CMF). South African patients were randomised using sealed envelopes. The envelopes were supplied for each stratification by the NCI. Upon reaching a cumulative doxorubicin dosage of 500 mg/m^2 in either regimen, CMF was utilised in all further therapeutic courses. In patients aged 65 years or more the dosage of 5-fluorouracil was reduced in CAF and CMF to 400 mg/m^2 intravenously days 1 and 8, and the dosage of methotrexate was reduced to 30 mg/m^2 intravenously days 1 and 8.

B122 and B141

In both B122 and B141 a treatment delay of up to 2 weeks was allowed for each cycle if necessary for the white blood cell (WBC) count to become greater than or equal to 4000/μl or the platelet count to become greater or equal to 100 000/μl. Drug modifications for both studies were the same, as were clinical laboratory and radiology exams [1, 2].

The pretreatment characteristics and stratification of patients and a comparison of baseline values between B122 and B141 are shown in Table 1. Table 2 shows analysis of continuous pretreatment variables and a comparison of the continuous baseline variables between B122 and B141. The described number of patients in the current studies equals that evaluated in the original studies. No postprotocol treatment was dictated, but patients who failed CMF in B122 usually received anthracyclines as part of their subsequent treatment, while those on the CAF or DAV/CMF treatment seldom received further anthracycline treatment. All patients were, however, followed for survival.

Statistical methods

Continuous baseline variables were compared using two-sample *t* tests and Wilcoxon rank sum tests. Cateogorical variables were compared using Pearson's χ^2 test and where appropriate, Fisher's exact test for 2 by 2 tables. Survival curves were

Table 2. Analysis of continuous pretreatment variables: a comparison of the continuous baseline variables between B122 and B141

Variables	B122 n	B122 Mean (S.D.)	B141 n	B141 Mean (S.D.)	P*
Age at on study	78	49.9 (10.62)	94	53.0 (9.35)	0.04 (0.066)
Disease-free interval	77	2.10 (3.13)	94	2.52 (2.66)	0.34 (0.041)
Performance status (Karnofsky)	78	85.1 (14.69)	86	84.2 (15.73)	0.69 (0.798)
No. of sites	78	2.38 (1.11)	94	1.91 (0.95)	0.00 (0.004)
Postmenopausal interval	72	5.11 (6.11)	92	7.00 (6.60)	0.06 (0.016)
Time from recurrence to on study	77	0.70 (1.80)	94	0.63 (1.61)	0.78 (0.106)

*Wilcoxon *t* test.

modelled by Kaplan–Meier estimates. Survival curves were compared using both the logrank and Wilcoxon test statistic. Comparisons of survival were made within stratum and adjusted over strata using adjusted logrank and Wilcoxon test statistics. Multivariate analysis was done using Cox's proportional hazards regression. Both forward and backward stepwise regression was used to select the best fitting models. Statistical analysis was done using the procedures PROC LIFETEST and PROC PHGLM in the SAS statistics package.

Table 3. Survival and response rates (95% confidence interval between treatments in B122 and B141

	B122		B141	
	CAF	CMF	CAF	DAV
Patients	38	40	46	48
Events	36	38	39	41
Censored	2	2	7	6
Survival (mo)				
75%	11.8 (7.2–17.5)	8.6 (7.0–13.9)	12.1 (9.1–17.3)	12.6 (9.7–18.0)
Median	20.9 (17.7–30.0)	16.8 (13.0–19.8)	22.6 (16.4–32.4)	24.4 (17.9–38.9)
25%	35.2 (25.6–55.3)	27.3 (19.3–43.0)	52.1 (32.1–86.9)	52.8 (37.9–100.5)
Survival rate				
3-yr	22.6%	19.0%	31.2%	40.8%
5-yr	11.3%	5.4%	24.3%	21.6%
Response				
Complete	7 (18.4%)	3 (7.5%)	6 (13.0%)	5 (10.4%)
Partial	23 (60.5%)	21 (52.5%)	24 (52.2%)	29 (60.4%)
Improvement	1 (2.6%)	0 (0.0%)	2 (4.4%)	3 (6.3%)
No change	5 (13.2%)	6 (15.0%)	9 (19.6%)	8 (16.7%)
Progression	2 (5.3%)	10 (25.0%)	4 (8.7%)	3 (6.2%)
Not evaluable	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)
P (Kruskal-Wallis)	0.02		0.80	

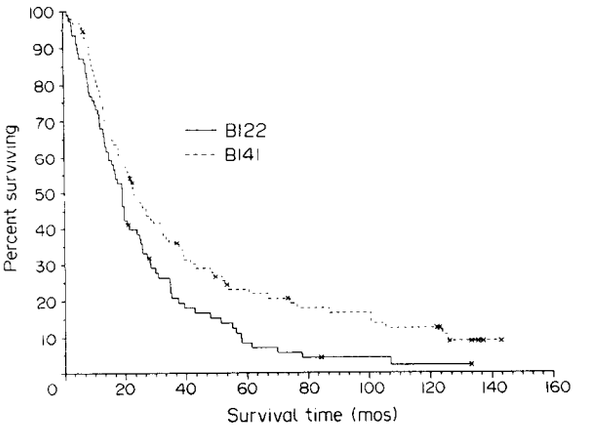

Fig. 1. Survival curves of B122 and B141.

RESULTS

The median survival of patients by treatment was 16.8 months with CMF, 20.9 months with CAF (B122 study), 22.6 months with CAF (B141 study) and 22.4 months with DAV/CMF. (The projected median survival times in the original publication on B122 with CMF was 17 months and with CAF, 27.2 months [1]. The analysis was performed while many subjects were still living. The manuscript quotes 24 of the 38 CAF subjects still alive, and 13 of the individuals receiving CMF as still living. Of the 24 CAF subjects censored at that point, 16 had not even been on study for 20 months. 9 of the 13 CMF subjects had been censored at on study times of less than 20 months.) The difference in median survival times between CAF and CMF in this long-term study of B122 still shows an interesting trend in favour of CAF, though this is not statistically significant. There is no difference in median survival between the subjects on the CAF regimen and the subjects on DAV/CMF in B141.

The 3-year and 5-year survival rates show that CAF was clinically superior to CMF (B122) and that DAV/CMF was clinically superior to CAF at 3 years though this difference was not statistically significant. This possible advantage also did not persist at 5 years. The 3-year survival rates varied from 19% with CMF to 22.6 and 31.2% with CAF but a 3-year survival rate of 40.8% was achieved with DAV/CMF. These results as well as the 25% and 75% survival rates are shown in Table 3. The survival curves for B122 and B141 are shown in Fig. 1. The median survival times on the two studies were 19.2 months on B122 and 22.6 months on B141. The number surviving at 3,

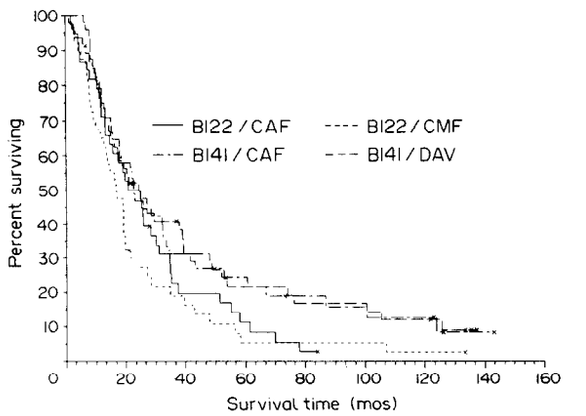

Fig. 2. Survival in the four treatment arms.

Table 4. Patients surviving

	Eligible and evaluable	Alive at 3 yr	5 yr	10 yr	15 yr*
B122	78	15	6	1	0
CAF	38	8	4	0	0
CMF	40	7	2	1	0
B141	94	32	18	9	0
CAF	46	14	9	4	0
DAV/CMF	48	18	9	5	0

*Several subjects were censored, thus 0 subjects alive at 15 years does not imply that all subjects have died by 15 years. Among patients entered from South Africa, on B122, 1 patient treated with CMF is alive at 15 years, and on B141, 2 patients treated with DAV/CMF and 1 patient treated with CAF are alive at 15 years (see Table 3).

5, 10 and 15 years for each treatment are shown in Table 4. The differences in the survival curves between the two studies is entirely explicable by the differences in patient prognostic factors. The survival rates of all 4 treatment arms are shown in Fig. 2. The number of surviving patients at 3, 5, 10 and 15 years are shown. Several subjects were censored, thus 0 subjects alive at 15 years does not imply that all subjects have died by 15 years.

Study factors significantly associated with a better survival were longer disease-free interval before entry on study, better performance status (PS), longer time from menopause and the number of involved sites. In study B141 the type of metastases, number of sites and PS were significant.

The survival data was analysed by both treatment and patient discriminants for both protocols. When analysed by each of the discriminants in turn, no subset of patients in B122 showed a statistically significantly better survival rate on CAF or CMF. In B141 patients with two organ sites of metastatic involvement had a significant median survival advantage of 39.36 months with DAV/CMF compared to 12.7 months on CAF ($P = 0.01$, Wilcoxon, $P = 0.02$, logrank). This survival advantage was not, however, seen in patients with one or with three or more involved organ sites.

Multivariate survival analysis of data in B122 showed that long disease-free intervals indicated longer survival than short disease-free intervals, few sites indicated longer survival than several sites and a poor pretreatment PS indicated shorter survival than a good pretreatment PS. In no model was treatment a signficant covariate either alone or in combination with other factors.

Multivariate survival analysis of the data in B141 showed that better PS was associated with longer survivals, patients with several sites tended to have poorer survival than patients with fewer sites and that patients with visceral disease also had a poorer survival than patients with osseous or soft tissue metastases. Treatment did not prove to be a significant covariate in any model examined.

DISCUSSION

Chemotherapy combinations give a better response rate and survival than single agents in the treatment of patients with advanced breast cancer [5, 6]. Combination chemotherapy is also superior to sequential single agents [7, 8]. Most studies have shown better response rates with doxorubicin-containing regimens [9–12], but lack long-term follow-up to evaluate clearly survival advantages for the doxorubicin-containing regimens.

In our current report there is very little censoring of survival data and long-term survival data are presented so that, despite the relatively small size of the trials, better conclusions about survival time can be drawn. The difference in median survival times between CAF and CMF in study B122 shows a trend in favour of CAF, but this is not statistically significant. There is no difference in median survival between the subjects on the CAF regimen and the subjects on DAV/CMF in B141. This information, together with the previously known response rate advantage, continues to support the use of CAF as the more effective regimen. The response rate and median survival with CAF in B122 and B141 is similar to those documented by us in ECOG studies [13]. The median survival time with CAF is 20.9 months in B122, 22.6 months in B141 and 20.2 months in ECOG studies. Response rates obtained with different doxorubicin based regimens have been similar [2, 14]. We have recently shown that mitolactol treatment is associated with an important frequency of myelodysplasia and acute non-lymphatic leukaemia [15]. Despite some possible small therapeutic advantages for the DAV regimen as compared to the CAF regimen, we therefore do not recommend mitolactol for general use.

The effect of a variety of patient characteristics in patients with advanced breast cancer have been evaluated in several trials [4, 16–18]. PS, number of metastatic sites and site of dominant metastases usually have an impact on prognosis. These characteristics are important in the studies reported here. The better survival time of premenopausal women treated with doxurubicin regimens [19, 20] could not be examined in the current study because of the small number of premenopausal women in the two studies. Similarly, the large ECOG study shows age to be an independent prognostic discriminant [18] and this is not refuted by the current studies.

In the treatment of breast cancer, measurement of response rate and response duration are important evaluation criteria. However, survival data continue to be important and the most accurate means of assessing the value of therapeutic intervention. This current report is unique in that nearly complete, very long-term survival data on stratified randomised studies, designed to evaluate therapeutic intervention, are available. It shows that the advances in management obtained by doxorubicin-containing regimens have had a small but measurable impact on survival, and that known patient discriminants are not overridden by treatment regimens investigated in these studies. This finding is of great importance to all doctors treating patients with advanced breast cancer: it highlights the need for continued randomised stratified trials to seek treatments with better survival and not just better response rates.

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Epidermal Growth Factor Receptor Expression as a Prognostic Indicator in Breast Cancer

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The significance of epidermal growth factor receptor (EGFR) status as a prognostic indicator was investigated by a competitive binding assay in 135 primary breast cancer patients. 55 patients (41%) were EGFR positive and EGFR status was negatively correlated with oestrogen receptor (ER) status ($P < 0.01$). 5-year postoperative follow-up showed that relapse-free survival for EGFR positive patients was significantly worse than that for EGFR negative patients ($P < 0.05$). There was no difference between the two groups in tumour size, axillary node involvement, age and menopausal status. Analysis by axillary node status demonstrated the poor prognosis of the EGFR positive group in node positive patients. As yet, no difference in prognosis has been seen in node negative patients. A higher frequency of haematopoietic relapse was observed in EGFR positive patients. Simulataneous or sequential EGFR measurements in primary tumour and metastatic sites of 34 patients showed that expression of EGFR was more enhanced in metastatic sites.
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INTRODUCTION

ENHANCED EXPRESSION of growth factors and growth factor receptors is a possible prognostic indicator for various human tumours [1-3]. In breast cancer the expression of epidermal growth factor (EGF), transforming growth factor alpha (TGF-α) and EGF receptor (EGFR) is important in the growth of cancer cells. In addition, there is a strong inverse correlation between EGFR and oestrogen receptor (ER) status [4, 5]. However, patients with ER negative tumours have a worse prognosis than those with ER positive tumours [6]. Therefore, EGFR status may become an independent prognostic factor for primary breast cancer patients.

Sainsbury *et al.* first described the poor prognosis for patients with EGFR positive breast cancer compared with those who were EGFR negative [2]. However, a controversial report failed to demonstrate the prognostic significance of EGFR, regardless