Pergamon

European Journal of Cancer, Vol. 33, No. 13, pp. 2194–2197, 1997

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

PII: S0959-8049(97)00396-1

Original Paper

A Randomised Trial of Six Versus Twelve Courses of Chemotherapy in Metastatic Carcinoma of the Breast

R.K. Gregory, T.J. Powles, J.C. Chang and S. Ashley

Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, U.K.

Chemotherapy given to patients with metastatic carcinoma of the breast is palliative in intent. Longer regimens would be justified if there was a proven prolongation of symptom response or survival. We conducted a randomised trial to assess the survival of patients receiving up to six extra courses of chemotherapy compared with our conventional regimen of six courses. The patients received either VAC, VEC (vincristine, doxorubicin or epirubicin and cyclophosphamide) or MMM (mitozantrone, methotrexate and mitomycin C) therapy. Patients who had stable disease or were responding after six courses of chemotherapy were randomised to either stop or continue treatment for another six courses. Those patients receiving maintenance therapy had a significantly longer duration of response ($P < 0.02$) and a significantly longer progression-free survival ($P < 0.01$). However, there was no survival difference between the two groups. Furthermore, treatment toxicity, which was similar in the two groups, persisted for longer in the maintenance group. These results indicate no clinical advantage for giving maintenance chemotherapy in order to prolong survival of patients with metastatic breast cancer. © **1997 Published by Elsevier Science Ltd.**

Key words: metastatic carcinoma of the breast, chemotherapy, palliative chemotherapy and maintenance treatment

Eur J Cancer, Vol. 33, No. 13, pp. 2194–2197, 1997

INTRODUCTION

THE PROGNOSIS of patients with advanced carcinoma of the breast is poor. The median survival cited in most studies is less than 2 years [1–3]. Objective response to chemotherapy makes a significant contribution to symptom palliation but has not been shown to influence overall survival [4]. Because of the palliative intent and the cumulative toxicity of chemotherapy, longer courses of treatment would only be preferable if it caused an improvement in survival or symptom palliation.

There is very little published on the value of maintenance chemotherapy. Smalley randomised patients who had responded to CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, predisone) at 24 weeks to either continue treatment or to stop and restart treatment on relapse [5]. He found no demonstrable survival advantage with continued chemotherapy. This has been confirmed in other studies [6, 7]. However, several studies have demonstrated a significant increase in progression-free survival [7–9]. Two published studies have also demonstrated an increase in overall survival [8, 10]. In an Australian study, patients were randomised to continuous treatment until disease progression or to three courses of treatment repeated at progression. Patients randomised to continuous treatment had an improved progression-free survival and a trend towards improved overall survival.

We performed a prospective randomised trial to ascertain if maintenance chemotherapy conveyed a survival advantage in patients with advanced carcinoma of the breast. The issue of quality of life was not specifically addressed in this study.

PATIENTS AND METHODS

Between October 1987 and January 1994, 107 patients were enrolled in this study, 100 of whom were assessable for analysis. Eligibility criteria included assessable metastatic disease which had remained stable or had responded to six courses of chemotherapy, age less than 75 years, life expectancy greater than 6 weeks, no serious cardiac disease and considered to be psychologically fit for chemotherapy. Patients were randomised to a control group stopping after a

Correspondence to T.J. Powles.
Received 19 Dec. 1996; revised 24 Jul. 1997; accepted 1 Aug. 1997.

conventional duration of treatment of six courses or to a maintenance group receiving treatment up to a total of 12 courses. All patients had pretreatment investigations to assess the extent of disseminated disease, which were repeated after six courses and on completion of maintenance chemotherapy where applicable. Investigations included full clinical assessment; routine haematology, biochemistry and liver function tests; isotope bone scan, limited skeletal survey, chest radiograph and liver ultrasound scan. Abnormal investigations at the start of treatment were repeated after two courses in order to document response to treatment.

All patients received either MMM (mitozantrone 7 mg/m^2, mitomycin C 7 mg/m^2 and methotrexate 35 mg/m^2), VAC or VEC (vincristine 2 mg, doxorubicin 60 mg/m^2 or epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 3 weeks. All patients had routine haematology performed prior to and 10 days following each course. Toxicity was assessed according to WHO criteria. Response to treatment was defined according to International Union against Cancer criteria [11]. A complete response (CR) required the disappearance of all measurable disease, a partial response (PR) at least a 50% decrease in tumour measurement. Progressive disease was defined as a 25% or more increase in the size of one or more measurable lesions or the appearance of new lesions. If there was evidence of progressive disease or unacceptable toxicity, treatment was discontinued.

Differences in response and toxicity between the treatment groups were assessed by means of the Mann–Whitney test for trend. Where relevant, this was stratified according to the type of chemotherapy regimen. Survival was measured from the start of chemotherapy; the data were not censored when the patient started a new treatment regimen. Survival was compared using the lifetable method [12] and the log-rank test [13].

Table 1. Patients' characteristics

	Control	Maintenance
Patients (*n*)	52	48
Age median (range)	58 (33–73)	59 (30–75)
Menopausal status		
pre	13	8
post	36	38
unknown	3	2
Previous treatment		
Adjuvant		
endocrine	19	10
chemotherapy	2	1
Metastatic		
endocrine	32	33
chemotherapy	12	9
Trial treatment		
VAC/VEC	21	18
MMM	31	30
Sites of disease		
soft tissue	31	21
pulmonary	25	22
liver	19	16
bone	37	28
CNS	2	1
other	8	7
Response at randomisation		
complete response	1	0
partial response	39	38
no change	12	10

RESULTS

Patients characteristics are listed in Table 1. The two patient groups were comparable in age, previous treatment, previous chemotherapy and sites of disease.

Of the 107 patients randomised, 7 were unassessable for analysis on review of eligibility. Of the 100 assessable patients, 39 received VAC (8) or VEC (31) (21 control and 18 maintenance). There was a marginal imbalance, with patients continuing on maintenance treatment being more likely to have VAC than those randomised to stop. Sixty-one patients received MMM (31 control, 30 maintenance).

Of the 48 patients randomised to maintenance treatment, 3 patients had 7 courses, 8 had 8 courses, 9 had 9 courses, 6 had 10 courses, 5 had 11 courses and 17 patients completed the full 12 courses.

Forty of the 52 control patients (77%) and 38 of the 48 patients (79%) on maintenance therapy had achieved objective response at the time of randomisation, indicating that there was no difference in the level of response between the two groups at the time of randomisation. Of those who received maintenence treatment, only 3 had an increased response (2 patients went from PR to CR and one patient went from NC to PR).

Thirty-one patients in the maintenance arm stopped treatment before 12 courses, 17 because of progressive disease, 4 patients refused further treatment and 7 patients stopped because of side-effects of the chemotherapy. One patient died from metastatic carcinoma whilst on treatment and one patient stopped because of acute depression. In one case the reason for stopping was unknown.

The median duration of response (Figure 1) for the 48 responding patients randomised to continue with maintenance therapy was significantly longer (10 months) than for the 52 control patients only receiving six courses of treatment (7 months), $P = 0.02$. Similarly, the median progression-free survival (Figure 2) was longer for the maintenance group (10 months) than for the control group (7 months), $P = 0.01$. However the overall survival (Figure 3) for the 48 maintenance patients (median survival 13 months) was not significantly longer than for the control patients (median survival 10.5 months), $P = 0.3$.

There was no significant difference in non-haematological toxicity between the control and maintenance groups when stratified by the type of chemotherapy (Table 2). No significant difference in haematological toxicity was found

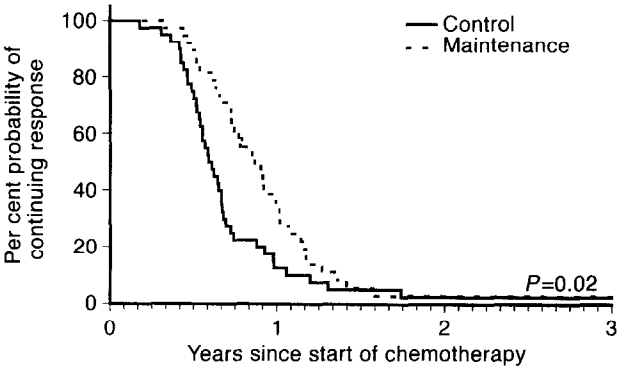

Figure 1. Duration of response for 52 control patients responding after receiving six courses of chemotherapy compared with 48 responding patients who continued maintenance therapy for up to a further 6 courses.

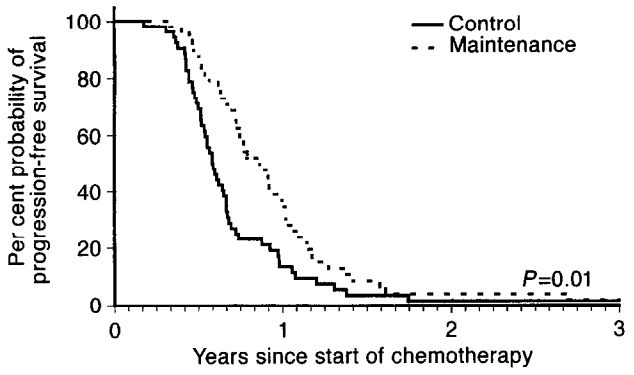

Figure 2. Progression free survival for 52 control patients receiving 6 courses of chemotherapy compared with 48 patients who continued maintenance therapy for up to a further 6 courses.

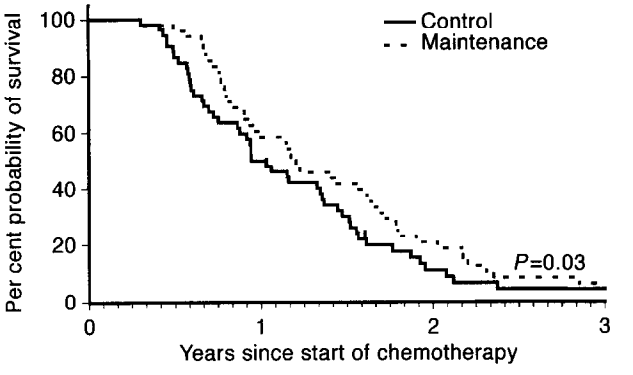

Figure 3. Survival of 52 control patients receiving 6 courses of chemotherapy compared to 48 patients who continued maintenance therapy for up to a further 6 courses.

between the control and maintenance groups receiving VAC/VEC treatment (Table 3), but surprisingly, Grade 3 leucopenia was more common in the control arm (46% compared with 21%). There were, however, significant differences between the two groups receiving MMM. Significantly higher grades of thrombocytopenia were seen in the maintenance group ($P<0.05$); on analysis there were no differences in thrombocytopenia after the initial six courses, implying that this is a problem of continuing treatment. Surprisingly, in the MMM group, there was a higher incidence of grade 3 anaemia in the control group (31% compared with 6%).

DISCUSSION

The results from this randomised trial of 6–12 courses of 3-weekly chemotherapy indicate no significant survival advantage associated with a more prolonged use of chemotherapy in metastatic carcinoma of the breast. However, there was a small but significantly increased duration of response and progression-free survival in those patients on maintenance therapy. This is consistent with reports from other groups who have demonstrated an increase in progression-free survival in the absence of an increase in overall survival [7, 9]. In contrast, a study randomising patients to either continuous treatment with mitoxantrone or four courses only found no difference in response duration or survival between the two groups [6]. However, this was a study using single-agent chemotherapy and it may be that the issue of acquired drug resistance was in part responsible for this result. One study has demonstrated a survival advantage with more prolonged courses of treatment [8]. 359 women with metastatic carcinoma of the breast were randomised to either 6/12 or 18/12 of FEC chemotherapy and both progression-free and overall survival were increased in the group receiving longer courses of treatment [8]. It may be that our prolonged course of treatment was not long enough to provide a survival advantage as the patients receiving 12 courses of treatment received a total of 9 months treatment, compared with 18/12 in Ejlertson's study [8].

It is possible that patients who previously had been exposed to chemotherapy might respond differently to maintenance therapy. To investigate this point, we stratified the duration of response, progression-free survival and overall survival curves by previous chemotherapy. The results were very similar to the group as a whole (duration of response: $P=0.03$; progression-free survival: $P=0.02$; overall survival $P=0.3$). Subsequent treatment might also be expected to influence the overall survival, although as patients changed treatment only on relapse this would not affect the progression-free survival. The patients in this study received a number of subsequent treatments of both chemotherapy and endocrine—of interest, in the control group randomised to stop, 20 patients went on to further chemotherapy on relapse compared with only 6 in the group randomised to maintenance therapy. This may reflect a perception by medical staff and patients that further chemotherapy would not be tolerated. It may also account for the lack of survival difference

Table 2. Non-haematological toxicity

	Control				Maintenance			
WHO grade	1	2	3	4	1	2	3	4
Nausea	36%	21%	6%	0	58%	33%	4%	0
Vomiting	17%	27%	4%	0	38%	25%	8%	0
Alopecia	17%	8%	25%	4%	58%	13%	21%	4%
Neuropathy	13%	12%	4%	0	29%	17%	0	0
Stomatitis	12%	6%	2%	0	13%	21%	0	0
Constipation	25%	4%	0	0	17%	0	0	0
Diarrhoea	13%	0	0	0	21%	4%	2%	2%
Lethargy	37%	44%	6%	2%	21%	67%	4%	0

The values represent the percentage of patients experiencing that grade of toxicity as the worst grade recorded over all courses of treatment.

Table 3. Haematological toxicity

	Conventional				Maintenance			
WHO grade	1	2	3	4	1	2	3	4
Anaemia								
VAC/VEC	63%	44%	0	0	48%	48%	0	0
MMM	67%	37%	31%	0	79%	67%	6%	0
Leucopenia								
VAC/VEC	17%	81%	46%	0	33%	98%	21%	0
MMM	37%	42%	63%	25%	40%	69%	77%	23%
Thrombocytopenia								
VAC/VEC	0	10%	0	0	0	10%	10%	0
MMM	6%	25%	12%	0	27%	35%	15%	0

The values represent the percentage of patients experiencing that grade of toxicity as the worst grade recorded over all courses of treatment.

between the two groups given that the group randomised to stop were more likely to receive a second and hence different chemotherapeutic regimen possibly overcoming the problem of acquired drug resistance and the treatment of *de novo* resistant clones.

The possibility of any symptom-free survival benefit from this small increased duration of response must be balanced against the detrimental effects of chemotherapy. In this study, we found no evidence of an increase in non-haematological toxicity nor clinical haematological problems, indicating that generally the patients were able to tolerate the more prolonged courses of treatment well. However, only 35% of those randomised to receive the maintenance treatment completed the full 12 courses. Half of these patients stopped due to progressive disease and the remainder for a variety of reasons, including toxicity from chemotherapy and refusal of further treatment. This may imply that in a number of cases the patients in conjunction with medical staff felt that the detrimental effects of chemotherapy had begun to outweigh the benefits.

Quality of life assessments would be required to further assess any small clinical benefit from maintenance therapy. Reports have indicated that continuing therapy is associated with improved quality of life. For example, an Australian trial which randomised patients to receive either continuous treatment until relapse or to have three cycles of treatment repeated at relapse found that quality of life was significantly worse in the group on intermittent treatment, possibly due to patient anxiety whilst off treatment [10]. There could be a number of possible explanations for this including the benefits of regular hospital contact, continued symptom control whilst on maintenance therapy and the reassurance to the patient provided by ongoing treatment.

In conclusion, these results indicate that longer periods of chemotherapy do not confer any survival benefit in patients with metastatic breast cancer in spite of a significantly longer disease-free and progression-free survival in patients on maintenance treatment. This is not surprising since we and others have previously shown that in spite of achieving high response rates, chemotherapy has generally failed to prolong survival in patients with metastatic breast cancer [4]. It therefore seems unlikely that continued maintenance therapy after 6 months treatment would be of any additional benefit for treatment of metastatic breast cancer, although in selected patients it may provide continuing symptom control.

1. Canellos GP. Combination chemotherapy for metastatic breast cancer. *Cancer* 1976, **38**, 1882–1886.
2. Twelves CJ. Breast cancer and liver metastases—incidence, diagnosis and outcome. *J R Soc Med* 1992, **85**, 808.
3. Overmeyer BA. Chemotherapeutic approaches in the treatment of breast cancer. *Semin Oncol* 1995, **22**(2, Suppl. 3), 2–9.
4. Powles TJ, Coombes RC, Smith IE. Failure of chemotherapy to prolong survival in a group of patients with metastatic carcinoma of the breast. *Lancet* 1980, **1**, 580–582.
5. Smalley RV, Murphy S, Hughley CM. Combination versus sequential five drug chemotherapy in metastatic carcinoma of the breast. *Cancer Res* 1976, **36**, 3911–3916.
6. Harris AL, Cantwell BMJ, Carmichael J, *et al.* Comparison of short-term and continuous chemotherapy for advanced breast cancer. *Lancet* 1990, **335**, 186–190.
7. Muss HB, Case LD, Richards F, *et al.* Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. *N Engl J Med* 1991, **325**, 1342–1348.
8. Ejlertsen B, Pfeiffer, Pedersen D, *et al.* Decreased efficacy of cyclophosphamide, epirubicin and 5-fluorouracil in metastatic breast cancer when reducing treatment duration from 18 to 6 months. *Eur J Cancer*, 1993, **29A**, 527–531.
9. Dixon AR, Jackson L, Chan SY, *et al.* Continuous chemotherapy in responsive metastatic breast cancer: a role for tumour markers. *Br J Cancer* 1993, **68**, 181–185.
10. Coates A, Gebski V, Stat M. Improving the quality of life during chemotherapy for advanced carcinoma of the breast. *N Engl J Med* 1987, **317**, 1490–1495.
11. Hayward JL, Carbone PP, Heuson JC. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977, **35**, 292–298.
12. Kaplan EL, Meier. Nonparametric estimation from incomplete observations. *J AM Stat Assoc* 1958, **53**, 457–481.
13. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.