Initial Paclitaxel Improves Outcome Compared With CMFP Combination Chemotherapy as Front-Line Therapy in Untreated Metastatic Breast Cancer

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Purpose: **To determine the place of single-agent paclitaxel compared with nonanthracycline combination chemotherapy as front-line therapy in metastatic breast cancer.**

Patients and Methods: **Patients with previously untreated metastatic breast cancer were randomized to receive either paclitaxel 200 mg/m² intravenously (IV) over 3 hours for eight cycles (24 weeks) or standard cyclophosphamide 100 mg/m²/d orally on days 1 to 14, methotrexate 40 mg/m² IV on days 1 and 8, fluorouracil 600 mg/m² IV on days 1 and 8, and prednisone 40 mg/m²/d orally on days 1 to 14 (CMFP) for six cycles (24 weeks) with epirubicin recommended as second-line therapy.**

Results: **A total of 209 eligible patients were randomized with a median survival duration of 17.3 months for paclitaxel and 13.9 months for CMFP. Multivariate analysis showed that patients who received paclitaxel survived significantly longer than those who received CMFP ($P = .025$). Paclitaxel produced significantly less severe leukopenia, thrombocytopenia, mucositis, documented infections (all $P < .001$), nausea or vomiting ($P = .003$), and fever without documented infection ($P = .007$), and less hospitalization for febrile neutropenia than did CMFP ($P = .001$). Alopecia, peripheral neuropathy, and myalgia or arthralgia were more severe with paclitaxel (all $P < .0001$). Overall, quality of life was similar for both treatments ($P \geq .07$).**

Conclusion: **Initial paclitaxel was associated with significantly less myelosuppression and fewer infections, with longer survival and similar quality of life and control of metastatic breast cancer compared with CMFP.**

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IN THE UNITED STATES each year, more than 180,000 women are diagnosed with breast cancer and more than 45,000 die of the disease.[1] Despite the major advances in adjuvant therapy, metastatic breast cancer remains a major clinical problem that affects large numbers of patients. For many years, standard chemotherapy combinations have been the mainstay of therapy for metastatic disease that is hormone resistant, estrogen receptor–negative, or with life-threatening or visceral disease. Initial chemotherapy has been either combinations of cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMFP) followed by anthracycline, or doxorubicin-containing combinations.[2-4] The choice of an appropriate initial chemotherapy is often limited by early relapse in patients who recently received adjuvant chemotherapy with the same combinations or by the condition of the patient. Thus, it is important to define the place of new anticancer drugs in breast cancer therapy.

When first described by Cooper,[5] CMFP-like combinations were reported with high response rates. When assessed using modern criteria and increasingly sophisticated imaging procedures, the CMFP regimen with or without vincristine produced objective responses in 37% to 68% of patients and median durations of response ranging from 6 to 11 months, with an associated median survival duration from initiation of treatment of 7 to 16 months.[6-15]

Doxorubicin alone has been shown to be as active as CMFP combinations in randomized studies in advanced breast cancer.[2,8,16] In these studies, doxorubicin produced shorter response duration when used as a single agent, but there was no clear difference in survival. Survival is difficult to interpret in these studies because patients were usually crossed over to the alternative regimen on progression.

Of six randomized studies that compared combinations of cyclophosphamide, doxorubicin, and fluorouracil with CMFP combinations in advanced breast cancer, three showed significantly higher response rates with the combination of cyclophosphamide, doxorubicin, and fluorouracil.[17-23] However, only two of six studies showed a statistically significant survival advantage for the doxorubicin combination. These studies have been interpreted as showing a slight advantage for doxorubicin combinations in metastatic breast cancer.[17] A recent meta-analysis of chemotherapy trials for metastatic breast cancer reviewed trials that compared anthracycline- versus nonanthracycline-based regimens.[24] Anthracycline

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combinations had higher response rates, but overall survival rates were similar. CMFP has been used as front-line therapy for metastatic breast cancer after early relapse from anthracycline-based adjuvant therapy, in the debilitated patient where palliation is the goal of therapy or by patient choice on consideration of side effects.

In an Australian randomized study, the combination of doxorubicin and cyclophosphamide was compared with CMFP in 305 previously untreated patients with metastatic breast cancer.[12] The response, response duration, and survival were similar between CMFP and doxorubicin/cyclophosphamide administered continuously until relapse. The doxorubicin combination was associated with significantly more nausea, vomiting, and alopecia compared with the CMFP combination. This experience provided an additional rationale for the use of CMFP as the control arm for our phase III randomized trial of CMFP compared with paclitaxel alone. CMF is a widely used combination in the adjuvant as well as the advanced setting, especially for good prognosis patients. Thus, the results of this comparison may have wider implications.

Paclitaxel is a novel cytotoxic agent that binds to the beta-tubulin monomer, inducing permanent microtubular polymerization.[25,26] The loss of dynamic reorganization of microtubules during mitosis results in selective block in the G_2/M phase of cell division. This action in vitro correlates with clinical activity.[27] Paclitaxel as a 24-hour infusion is active in previously untreated patients with advanced breast cancer.[28-33] The duration of paclitaxel infusion has varied, with other studies reporting 3-hour infusion schedules or, since our study was started, 1-hour infusions.[34-37] A large randomized European-Canadian study compared two doses of paclitaxel (135 mg/m^2 *v* 175 mg/m^2) and two infusion times (3 hours *v* 24 hours) in relapsed ovarian cancer. There was no difference in outcome detected between the two doses or infusion rates. The incidence of hypersensitivity reactions on this study was low and not influenced by the dose or schedule. However, this study clearly demonstrated that the 24-hour paclitaxel infusion was associated with a significantly greater reduction in neutrophils after each course compared with the 3-hour infusion.[34] This observation has been confirmed by another recent randomized study that compared 3-, 6-, and 24-hour infusions.[38] On the basis of this evidence and its convenience, the 3-hour schedule was chosen for this trial. Subsequently, a randomized phase III trial of 3- versus 96-hour infusions of paclitaxel has demonstrated no differences in outcomes in metastatic breast cancer.[39]

At the time this trial was initiated, it was unclear whether the dose of paclitaxel was important in metastatic breast cancer. However, early studies reported high response rates at 200-mg/m^2 and 250-mg/m^2 doses of paclitaxel as a 24-hour infusion, providing a rationale for the paclitaxel dose of 200 mg/m^2 for this trial.[40,41] Subsequently, Nabholtz et al[42] suggested that a 175-mg/m^2 dose of paclitaxel may prolong time to progression compared with a dose of 135 mg/m^2.

PATIENTS AND METHODS

Patients

Eligible patients with histologically proven metastatic or locally advanced breast cancer (stage III or IV) or recurrent breast cancer after surgery, prior radiotherapy more than 4 weeks previously, or prior adjuvant chemotherapy more than 6 months earlier, but no prior chemotherapy for advanced disease, were entered onto the trial. Requirements included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; disease measurable or assessable for response; adequate prior bone marrow, liver, and renal function; a life expectancy of at least 3 months; and written informed consent. Patients not eligible for the trial were those with a history of or current malignancy other than breast cancer, except nonmelanoma skin cancer or carcinoma-in-situ of the cervix, a history of cardiac arrhythmias, congestive cardiac failure, documented myocardial infarction within the prior 6 months, World Health Organization (WHO) grade 2 or worse neuropathy, proven brain metastasis as sole evidence of metastasis, or dementia or altered mental status that would prohibit informed consent.[43]

Ethics Review

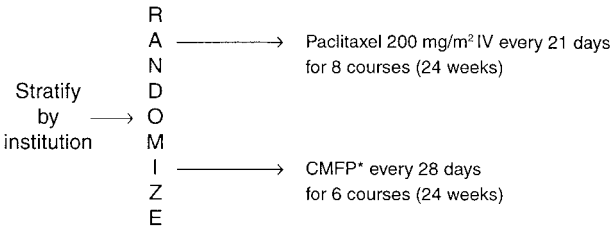
The protocol was approved by the institutional ethics committees of each participating institution. Written informed consent was obtained for each patient. All serious adverse reactions were reported to the study sponsor and to institutional ethics committees in accordance with their reporting requirements. The study was designed, conducted, analyzed, and reported in accordance with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*.[44]

Toxicity and Response Criteria

Standard WHO toxicity and response criteria were used.[43] Quality of life (QOL) was assessed using QOL linear analog scales completed by the patient and the Spitzer QOL index completed by the physician.[12,45]

Treatment

Patients were stratified by institution and randomized to receive either paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) 200 mg/m^2 intravenously (IV) infused over 3 hours every 21 days for eight courses (24 weeks) or cyclophosphamide 100 mg/m^2/d orally on days 1 to 14, methotrexate 40 mg/m^2 IV on days 1 and 8, fluorouracil 600 mg/m^2 IV on days 1 and 8, and prednisone 40 mg/m^2/d orally on days 1 to 14 repeated every 28 days for six courses (24 weeks; Fig 1). Patients who received paclitaxel were given premedication with dexamethasone 20 mg orally 12 hours and again 6 hours before chemotherapy. Diphenhydramine 50 mg IV (or promethazine 25 mg) and cimetidine 300 mg IV (or ranitidine 50 mg IV) were administered 30 minutes before chemotherapy. Antiemetics were subsequently administered at the investigator's discretion. Patients whose disease progressed while receiving front-line therapy were recommended to receive epirubicin 90



* Cyclophosphamide 100 mg/m² PO Days 1 to 14
Methotrexate 40 mg/m² IV Days 1 and 8
5-Fluorouracil 600 mg/m² IV Days 1 and 8
Prednisone 40 mg/m² PO Days 1 to 14

Fig 1. Treatment schema.

mg/m^2 IV every 3 weeks. After 6 months of initial chemotherapy, patients with stable disease or objective response were to be monitored off therapy until relapse.

Dose Modification

Dose modifications were based on nadir counts, with 25% dose reductions for absolute neutrophil count less than 0.5×10^9/L, platelet count less than 50×10^9/L, and/or febrile neutropenia (fever > 38°C with absolute neutrophil count $< 0.5 \times 10^9$/L) or significant thrombocytopenic bleeding. Patients with an absolute neutrophil count less than 1.5×10^9/L or a platelet count less than 100×10^9/L at scheduled re-treatment dates were required to have a weekly delay until recovery with dose adjustment based on nadir counts.

All WHO grade 3 nonhematologic toxicities (except alopecia and nausea/vomiting) required 25% dose reduction. Any patient who experienced WHO grade 4 nonhematologic toxicity was to be taken off study. Patients with symptomatic arrhythmia or atrioventricular block were to cease treatment. Patients with hypersensitivity reactions with hypotension, angioedema, respiratory distress, or generalized urticaria were to have their paclitaxel infusion stopped and hypersensitivity medically managed.

Investigations

Scheduled investigations included complete blood examination, which was performed before treatment and weekly thereafter. Urea analysis, electrolyte analysis, liver function tests, WHO toxicity rating, physical examination, and QOL assessments were performed before treatment and subsequently with each course of treatment. Investigations to establish and monitor metastatic disease included computed tomography scan, bone scan, and radiographs before therapy, with tests repeated after 12 weeks and 24 weeks on therapy. These tests were also repeated at the time of suspected relapse or progression and at intervals no less than 4 weeks apart when confirming a partial or complete response. After completion of treatment, patients were monitored monthly until relapse, and thereafter their status was obtained at 3-month intervals until death or study analysis.

Statistical Methods

The target accrual was 200 patients. Patients were stratified by participating center before randomization. Computer-generated randomization charts were prepared for each center and held at the Statistical Centre at Peter MacCallum Cancer Institute, Melbourne, Australia. Randomization was based on an adaptive biased coin procedure with a bias of 3^n at each allocation in favor of the arm with n fewer patients. All data were collected by institutional data managers, checked by sponsoring company monitors and at the trial center, and entered on a database at the Statistical Centre.

One planned interim analysis was conducted after 23 patients were accrued to each arm to check that the response rate was at least 25% for each treatment arm. The results were not released to the investigators. A second interim analysis was conducted on the first 100 patients for a conference presentation, but this took place after completion of accrual of all patients onto the trial. The emerging data from this analysis, therefore, would not have affected either the accrual or the interpretation of the final results of the trial.

All major end points were compared using intention-to-treat analyses that included all randomized patients. Response rates in the two arms were compared using a two-sided Fisher's exact test with StatXact 3 for Windows (Cytel Software Corp, Cambridge, MA). Progression-free and overall survival rates were estimated according to the Kaplan-Meier product-limit method, using S-PLUS version 3.3 for Windows (StatSci, Seattle, WA). Time was measured from the date of randomization and the close-out date for all survival analyses was February 20, 1997. All deaths were counted as events in the overall survival analyses, and both progressions and deaths without progression in the progression-free survival curves. The Brookmeyer-Crowley method was used to estimate 95% confidence intervals for median survival times. Differences between groups were tested using the Mantel-Cox log-rank test (S-PLUS version 3.3 for Windows).

Categories of toxicity were compared between the two randomization arms using the Cochran-Armitage test for linear trend with exact inference, two-sided, unless otherwise specified (StatXact 3 for Windows). Disease sites were classified into skin and soft tissue, bone, liver, lung (including pleural effusions), and other visceral (including brain).

Prognostic factors were tested in univariate analyses of response, progression-free survival, and overall survival. These included ECOG performance status, extent of disease, menopausal status at diagnosis, time since diagnosis, prior adjuvant chemotherapy, prior radiotherapy, and prior hormone therapy. Multivariate analyses were performed on the aforementioned factors plus randomization arm, using logistic regression for analysis of response (LogXact for Windows; Cytel) and the Cox proportional hazards model for survival analyses (SPSS Advanced Statistics 7.5, SPSS Inc, Chicago, IL).

QOL was assessed before the commencement of treatment and after each course. The QOL instruments were those previously published and validated by many of the investigators in this study.[12,45] At each assessment, the patient marked six linear analog scales (physical well-being, mood, pain, nausea/vomiting, appetite, overall QOL), and the physician completed the Spitzer QOL index that consisted of five questions, each scored 1 to 3. The Wilcoxon rank sum test was used to compare the treatment arms for the average improvement in each measure of QOL while on treatment relative to the baseline values.[46]

RESULTS

A total of 209 patients were accrued from 17 centers in Australia and New Zealand: 107 were randomized to receive paclitaxel, and 102 were randomized to receive CMFP. The median age of patients was 54 years on both arms (ranges: paclitaxel, 36 to 73 years; CMFP, 32 to 80 years).

Patient characteristics at randomization are listed in Table 1. At trial entry, 31% of patients on the paclitaxel arm and 40% of patients on the CMFP arm had an ECOG performance status of 0. Only 21% of paclitaxel patients and 33%

Table 1. Patient Characteristics at Randomization by Treatment Arm

	% Paclitaxel (n = 107)	% CMFP (n = 102)
ECOG performance status		
0	31	40
1	60	48
2	9	12
Site of disease*		
Skin/soft tissue	53	51
Bone	65	58
Liver	46	47
Lung	40	39
Other visceral	13	11
Dominant site of disease		
Skin/soft tissue only	7	14
Bone ± skin/soft tissue	18	16
Visceral ± bone ± skin/soft tissue	75	71
Menopausal status at diagnosis		
Premenopausal	47	48
Peri/postmenopausal	52	52
Unknown	1	0
Time since diagnosis, years		
≤ 3	47	50
> 3	53	50
Estrogen receptor status		
Positive	40	37
Negative or borderline	30	19
Unknown	30	44
Progesterone receptor status		
Positive	29	25
Negative or borderline	34	21
Unknown	37	54
Prior adjuvant chemotherapy		
None	79	67
CMF (vincristine) (prednisolone)	21	29
CMF (doxorubicin)	0	1
Other	0	2
Unknown	0	1
Other prior therapy*		
Adjuvant radiotherapy	39	48
Palliative radiotherapy	42	39
Endocrine therapy	72	77

*Each patient could have more than one site.

of CMFP patients had received prior adjuvant chemotherapy. Five completed their adjuvant therapy between 9 and 12 months, and the remainder more than 12 months before randomization. Seventy-two percent of paclitaxel patients and 77% of CMFP patients had received prior endocrine therapy. The trial opened for accrual in September 1993, and the median follow-up for patients still alive at the close-out date was 26 months (range, 17 to 40 months).

Two paclitaxel patients and three CMFP patients did not receive any of their randomized treatment. Dose reductions of more than 5% occurred in 23% of treated paclitaxel patients and 32% of CMFP patients. Nine percent of paclitaxel patients had a delay of ≥ 1 week, whereas 34% of CMFP patients experienced a similar delay. Forty-eight percent of paclitaxel patients and 52% of CMFP patients completed 24 weeks of treatment.

Complete response occurred in 2% of paclitaxel patients and 6% of CMFP patients. Partial response occurred in 27% of paclitaxel patients and 29% of CMFP patients. The overall objective response rates for paclitaxel and CMFP were 29% (95% confidence interval [CI], 21% to 39%) and 35% (95% CI, 26% to 45%), respectively ($P = .37$; Table 2). Stable disease was noted in 37% of patients who received paclitaxel and 32% who received CMFP. Potential prognostic factors were studied to determine whether they influenced response rates. Only patients who were premenopausal at diagnosis had significantly higher response rates than peri/postmenopausal women ($P = .008$). However, there was still no significant difference between treatment arms ($P = .44$) when adjusted for menopausal status in a multivariate logistic regression model. No other on-study factors had a significant influence on response rates. The response rate of CMFP patients who had received prior adjuvant CMF was not significantly different from those who had not ($P = .66$).

Only 4% of paclitaxel patients and 3% of CMFP patients were alive without progression at the close-out date. The estimated median time to progression for paclitaxel patients was 5.3 months (95% CI, 4.1 to 5.6 months), with 15% progression-free at 1 year and 3% at 2 years. The estimated median time to progression for CMFP patients was 6.4 months (95% CI, 5.2 to 7.8 months), with 17% progression-free at 1 year and 5% at 2 years. There was no significant difference between the treatment arms ($P = .25$; Fig 2 and Table 2). Univariate analyses of prognostic factors that affect progression-free survival showed that patients with an ECOG performance status of 0 ($P = .024$) or more than 3 years since diagnosis ($P = .002$) had significantly longer

Table 2. Summary of Results by Treatment Arm

	Paclitaxel (n = 107)		CMFP (n = 102)		
	%	95% CI	%	95% CI	*P*
Response rate (complete + partial)	29	21-39	35	26-45	.37
Progression-free survival					
Estimated median (months)	5.3	4.1-5.6	6.4	5.2-7.8	
Surviving progression-free at 1 year	15	8-22	17	9-24	.25
Surviving progression-free at 2 years	3	0-8	5	1-9	
Overall survival					
Estimated median (months)	17.3	12.6-21.4	13.9	11.4-16.5	
Surviving at 1 year	61	52-70	55	45-65	.068
Surviving at 2 years	39	29-48	20	12-29	

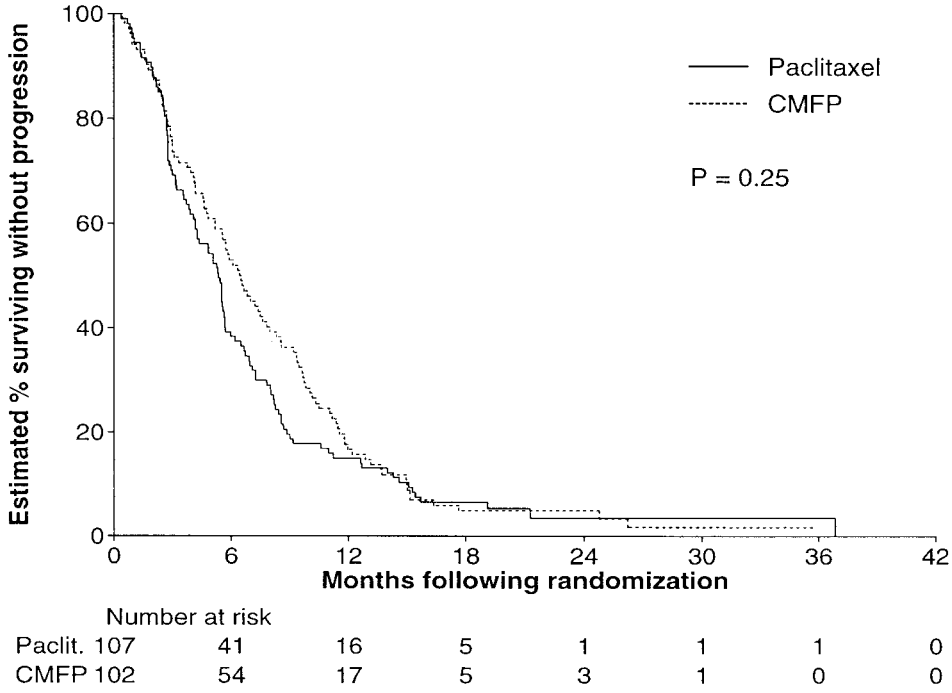


Fig 2. Progression-free survival by treatment arm.

progression-free survival. In the multivariate model that contained these two factors, there remained no significant difference between the treatment arms ($P = .23$).

There were 30% of paclitaxel patients and 20% of CMFP patients still alive at the close-out date. The estimated median survival duration was 17.3 months (95% CI, 12.6 to 21.4 months) for paclitaxel patients with 61% alive at 1 year and 39% at 2 years. The estimated median survival of CMFP patients was 13.9 months (95% CI, 11.4 to 16.5 months), with 55% alive at 1 year and 20% at 2 years. The difference between the two treatment arms was not statistically significant ($P = .068$; Fig 3 and Table 2).

Univariate analysis of on-study factors showed that patients with an ECOG performance status of 0 ($P = .002$), nonvisceral disease ($P = .0003$), or diagnosis more than 3 years before randomization ($P = .002$), had significantly better survival. For example, patients with an ECOG performance status of 0 had a median survival duration of 20.0 months compared with only 12.6 months for patients with a performance status of 1 or 2. Multivariate analysis confirmed the importance of these factors (Table 3). In this model, patients on the initial paclitaxel arm had significantly improved survival compared with those on the CMFP arm ($P = .025$). There were no important interactions between the three significant prognostic factors and the treatment arms.

Leukopenia, thrombocytopenia, nausea and vomiting, and mucositis were all significantly less severe with paclitaxel compared with CMFP (Table 4). Febrile neutropenia and/or infection occurred in 10% of paclitaxel patients and 27% of CMFP patients ($P = .001$). The mean duration of admission for febrile neutropenia or infection was 1.5 days for paclitaxel and 4.4 days for CMFP ($P = .0006$). Overall, 1.6% of paclitaxel courses and 8.2% of CMFP courses required hospitalization for febrile neutropenia and/or documented infection. Alopecia, myalgia/arthralgia, and peripheral neuropathy were significantly more severe with paclitaxel compared with CMFP ($P < .0001$). WHO grade 3 peripheral neuropathy occurred in 9% of paclitaxel patients, and grade 4 occurred in 1%. Only three patients experienced hypersensitivity reactions with hypotension while receiving paclitaxel treatment and without sequelae.

QOL was assessed at study entry and after every treatment course. The average QOL over all courses was calculated and subtracted from the baseline value. Both the patient's and physician's assessment of QOL were recorded. Most measures of QOL (except pain) were slightly better with paclitaxel than with CMFP, but the differences were not statistically significant ($P \geq .07$ for all measures; Fig 4).

Thirty-three patients who received initial paclitaxel and 31 who received CMFP underwent no further chemotherapy (Table 5). Similar numbers of patients on both arms received second-line anthracycline (43 paclitaxel patients; 39 CMFP patients). An objective response to second-line anthracycline-based chemotherapy occurred in 33% of patients on the paclitaxel arm and 21% on the CMFP arm. Patients who initially received paclitaxel with anthracycline second-line chemotherapy had an estimated median survival duration of

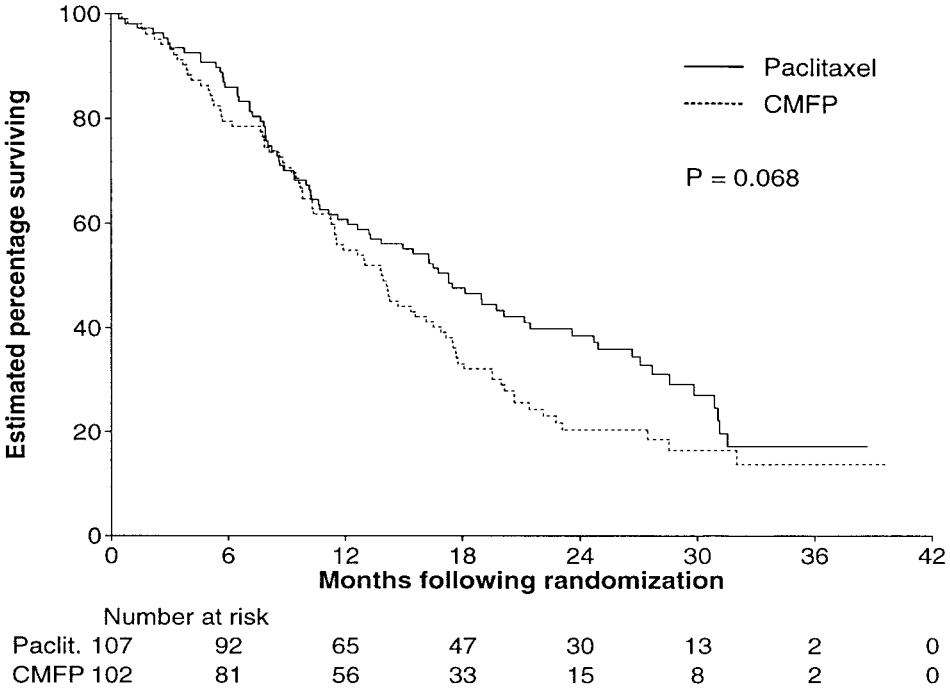


Fig 3. Overall survival by treatment arm.

13.3 months from the initiation of second-line chemotherapy, whereas patients who originally received CMFP had an estimated median survival duration of 5.5 months. Because the selection of patients for second-line therapy was subject to bias, statistical comparison was not performed on these two outcomes.

DISCUSSION

These results show that initial paclitaxel alone produces tumor control comparable to that with CMFP combination chemotherapy, with similar objective response and time to progression. The response rate for paclitaxel is similar to those previously reported for single-agent paclitaxel administered as a 3-hour infusion. The response rate for CMFP seems low but is within the range previously reported in the literature, and the 95% CI for response to CMFP in this trial suggests that the objective response rate is between 26% and 45%. The response rates may reflect the more intensive and sophisticated imaging techniques applied in modern cancer trials and the difficulty in discerning change in bone lesions. Perhaps more importantly, the median time to progression and survival on CMFP is similar to that previously reported with this combination in Australia and elsewhere.[2-4,6-14]

Table 3. Cox Proportional Hazards Model of Factors That Influence Survival

Factor	Reference Group	Relative Death Rate		*P*
		Estimate	95% CI	
≤ 3 years since diagnosis	> 3 years	2.0	1.4-2.8	< .0001
ECOG performance status 1-2	0	2.0	1.4-2.8	.0001
Visceral disease	Nonvisceral	2.0	1.3-2.9	.0003
Paclitaxel	CMFP	0.7	0.5-1.0	.025

In the univariate analysis, overall survival was slightly longer on the paclitaxel arm, but the difference was not statistically significant ($P = .068$). The trial randomization was stratified by institution but not for each of the seven potential prognostic factors, three of which were shown to have a significant influence on survival in this trial. Adjusting for these factors, Cox proportional hazards regression showed that patients on the paclitaxel treatment arm had significantly improved survival ($P = .025$). The prolongation of survival seemed to be clinically meaningful, with a median survival duration of 17.3 months with paclitaxel and 13.9 months with CMFP, and a relative death rate (paclitaxel/CMFP) of 0.70 after adjustment for prognostic factors. This improvement in survival seemed to be of value to patients, with a 19% improvement in survival at 2 years. However, because the initial tumor control rates are similar, the improvement in survival may reflect a more optimal sequence of therapy starting with paclitaxel.

Weekly blood counts were obtained to provide an accurate picture of the comparative myelosuppression of the two arms. Paclitaxel caused significantly less leukopenia and thrombocytopenia. Neutropenia was similar between the two arms, whereas the number of infections, hospitalization

Table 4. Comparison of Acute Toxicities Between Treatment Arms*

Worst WHO Grade†	% of Patients With Each Grade					*P*
	0	1	2	3	4	
Leukopenia						
Paclitaxel	11	18	42	23	6	< .0001
CMFP	4	12	17	42	24	
Neutropenia						
Paclitaxel	8	9	17	28	39	.91
CMFP	11	5	10	35	38	
Thrombocytopenia						
Paclitaxel	98	1	0	0	1	< .0001
CMFP	74	8	6	8	4	
Nausea/vomiting						
Paclitaxel	63	21	15	1	0	.0032
CMFP	41	34	16	8	0	
Mucositis						
Paclitaxel	70	19	9	3	0	.0002
CMFP	43	28	22	6	0	
Peripheral neuropathy						
Paclitaxel	23	37	30	9	1	
CMFP	98	2	0	0	0	< .0001
Myalgia/arthralgia						
Paclitaxel	27	19	34	20	0	
CMFP	95	1	3	1	0	< .0001
Alopecia						
Paclitaxel	5	1	18	76	—	
CMFP	22	25	28	24	—	< .0001
Documented infection						
Paclitaxel	95	3	1	1	0	.0006
CMFP	81	6	6	2	5	
Fever without documented infection						
Paclitaxel	92	3	4	1	0	.0069
CMFP	83	2	6	5	4	

*Five untreated patients were omitted.

†The worst WHO grade toxicity each patient experienced.

for infection, and duration of hospitalization were much less with paclitaxel than with CMFP. A possible explanation is that CMFP was associated with significantly more mucositis, thus providing a portal of entry of infection. In addition, the duration of neutropenia with paclitaxel was considerably shorter, as indicated by the number of patients who required treatment delays. Alopecia, myalgia, and peripheral neuropathy were significantly more pronounced with paclitaxel. The latter was grade 3 or 4 in only 10% of patients.

Overall, the QOL on both arms seemed acceptable to patients and was not significantly different. Patients were asked to score overall QOL on both treatments and would have considered general tolerance of the side effects as well as symptoms related to disease. With the exception of pain, patients on the paclitaxel arm experienced slightly better QOL for each parameter during treatment than patients on the CMFP arm.

Although this trial is the first comparison of paclitaxel monotherapy and CMFP as front-line chemotherapy for metastatic disease, the preliminary results of two other trials help to put this trial in context.[47-49] Sledge et al[48] from the ECOG compared single-agent paclitaxel at 175 mg/m^2 over 24 hours with doxorubicin and the combination of doxorubicin plus paclitaxel in a randomized trial in previously untreated patients with metastatic breast cancer. In that study, the objective response rate for paclitaxel monotherapy was 34%, and the median time to progression was 6 months. Their results are similar to the results reported in our study. In the ECOG trial, comparison of the two single agents, paclitaxel and doxorubicin, produced similar response, time to progression, and survival. However, cross-over occurred on both monotherapy arms.

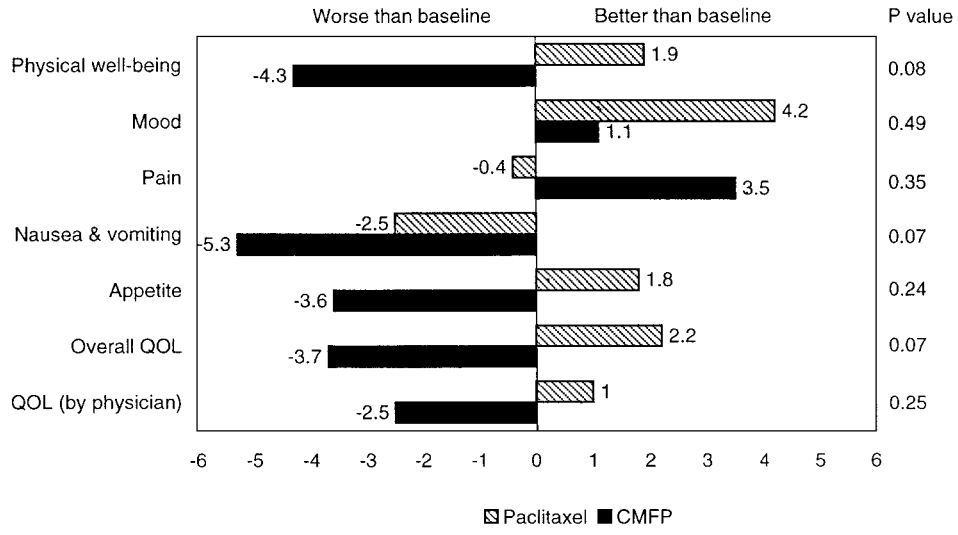


Fig 4. Average changes in QOL relative to baseline by treatment arm.

Table 5. Second-Line Chemotherapy*

	Initial Treatment	
	% Paclitaxel (n = 105)	% CMFP (n = 99)
Second-line chemotherapy		
None	31	31
Anthracycline-based	41	39
CMFP-like	18	12
Taxane	3	6
Other	7	11

*Five patients untreated after initial randomization was omitted.

In a study by Gianni et al,[50] 41% of patients with advanced breast cancer treated with the paclitaxel/doxorubicin combination achieved a complete response, with an overall objective response rate of 94% and a duration of response of 11 months for partial responders. Subsequent phase II studies reported response rates $\geq$ 58%.[47,51,52] In the aforementioned randomized ECOG study, the objective response rate with the paclitaxel/doxorubicin combination was 47%, with only 6% complete responses and a median time to progression of 8 months.[48] The survival on all three arms of the ECOG study was similar. In a conflicting preliminary report, the European Organization for Research and Treatment of Cancer breast group randomized trial obtained a better response and time to progression with single-agent doxorubicin than with paclitaxel monotherapy but equivalent survival and QOL, with more toxicity reported for the doxorubicin arm.[49]

The studies by the ECOG and European Organization for Research and Treatment of Cancer suggest that single-agent therapy with paclitaxel or doxorubicin with cross-over to the other agent is as effective as initial combination therapy when treating metastatic disease, although response rates and initial time to progression are inferior with monotherapy compared with the combination. The present study is the only one of these three in which cross-over to taxane did not occur, but rather a cross-over to anthracycline on both arms. Thus, this trial may suggest that the sequence of paclitaxel and then anthracycline may confer a survival advantage over the CMFP/anthracycline sequence. This has considerable implications for optimal sequences in adjuvant studies.

Bonadonna et al[53] reported the superiority of sequential blocks of doxorubicin and CMF in the poor-prognosis adjuvant setting compared with the cycle-by-cycle alternation of these two regimens. It has been suggested that the use of non–cross-resistant alternating chemotherapy is optimal for cell kill.[54-57] Our trial gives further insight into the optimal sequence of blocks of chemotherapy and suggests that paclitaxel followed by anthracycline may be a better sequence of therapy than CMFP followed by anthracycline, although the initial tumor control is similar. One hypothesis is that paclitaxel and doxorubicin are less cross-resistant than CMFP sequences. Thus, there may be optimal sequences for new regimens using blocks of chemotherapy, especially in the adjuvant setting. This hypothesis may be supported by preliminary results of the Cancer and Leukemia Group B intergroup adjuvant study, which show improved survival with a block of paclitaxel courses after initial treatment with doxorubicin/cyclophosphamide in node-positive breast cancer.[58] These data require further follow-up and confirmation.

CMFP has been used in debilitated patients who present with de novo metastatic breast cancer where the aim of therapy is palliation. This trial shows that paclitaxel is associated with less myelosuppression and fewer infections than CMFP, with fewer side effects that require hospitalization, equivalent initial tumor control, and, subsequently, clinically valuable, improved survival.

APPENDIX

Investigators and Data Managers of the Taxol Investigational Trials Group, Australia/New Zealand

The investigators and data managers who participated in this trial were as follows: *from Box Hill Hospital, Melbourne*: J. Chirgwin, D. Goldstein, M. Leyden, D. Hopkins, and A. McManus; *Dunedin Hospital, New Zealand*: M. Jeffery, D. Perez, and F. O'Hagan; *Heidelberg Repatriation General Hospital, Melbourne*: W. Cosolo, J. Zalcberg, A. Zimet, and M. D'Astoli; *Mater Misericordiae Hospital, Newcastle*: S. Ackland, A. Bonaventura, J. Stewart, J. Killmurray, and S. Freeman; *Monash Medical Centre, Melbourne*: G. Richardson, S. Hurran, and L. Seferth; *Palmerston North Hospital, New Zealand*: S. Allan, G. Forgeson, and G. Humm; *Peter MacCallum Cancer Institute, Melbourne*: P. Francis, M. Millward, D. Rischin, G. Toner, R. Maisano, M. Urch, and L. Sheeran; *Prince of Wales Hospital, Sydney*: B. Brigham, M. Friedlander, C. Lewis, M. Gleason, and E. George; *Princess Alexandra Hospital, Brisbane*: E. Walpole, V. Wardle, and A. Karanicolas; *Royal Adelaide Hospital, Adelaide*: I. Olver, F. Parnis, J. Russell, and N. Olszewski; *Royal Melbourne Hospital, Melbourne*: R. Basser, G. Goss, M. Green, and V. Wong; *Royal North Shore Hospital, Sydney*: D. Bell, J. Levi, H. Wheeler, and S. McCowatt; *Royal Prince Alfred Hospital, Sydney*: J. Bishop (study chairman), M. Boyer, A. Coates, M. Tattersall, and A. Childs; *Sir Charles Gairdner Hospital, Perth*: M. Buck, M. Byrne, J. Dewar, G. Van Hazel, and L. Donlevy; St Vincent's Hospital, Sydney: D. Dalley, J. Grygiel, R. Stuart-Harris, and D. Dalley; *Waikato Hospital, New Zealand*: I. Kennedy and J. Lee; and *Westmead Hospital, Sydney*: C. Crombie, H. Gurney, P. Harnett, R. Kefford, N. Amos, and B. Stuart-Harris.

Statistical Center (*from the Peter MacCallum Cancer Institute, Melbourne*): J. Smith (study statistician), J. Dipell, J. Matthews, F. Page, A. Rogers, and J. Stone.

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REFERENCES

1. Boring CC, Squires TS, Tong T: Cancer statistics. CA Cancer J Clin 42:19-38, 1992

2. Brambilla C, DeLena M, Rossi A, et al: Response and survival in advanced breast cancer after two non-cross-resistant combinations. BMJ 1:801-804, 1976

3. Canellos GP, Pocock SJ, Taylor SG, et al: Combination chemotherapy for metastatic breast carcinoma. Cancer 38:1882-1886, 1976

4. Tranum B, Hoogstraten B, Kennedy A, et al: Adriamycin in combination for the treatment of breast cancer. Cancer 41:2078-2083, 1978

5. Cooper RG: Combination chemotherapy in hormone resistant breast cancer. Proc Am Assoc Cancer Res 10:15, 1969 (abstr)

6. Muss HB, White DR, Cooper MR, et al: Combination chemotherapy in advanced breast cancer: A randomized trial comparing a three- vs a five-drug program. Arch Intern Med 137:1711-1714, 1977

7. Smalley RV, Murphy S, Huguley CM, et al: Combination versus sequential five-drug chemotherapy in metastatic carcinoma of the breast. Cancer Res 36:3911-3916, 1976

8. Hoogstraten B, George SL, Samal B, et al: Combination chemotherapy and Adriamycin in patients with advanced breast cancer: A Southwest Oncology Group study. Cancer 38:13-20, 1976

9. Cebon JS, Bishop JF, Harvey V, et al: Dose-intense weekly cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisolone (CMFP) in advanced breast cancer. Br J Cancer 61:133-136, 1990

10. Canellos GP, DeVita VT, Gold GL, et al: Combination chemotherapy for advanced breast cancer: Response and effect on survival. Ann Intern Med 84:389-392, 1976

11. Cummings FJ, Gelman R, Horton J: Comparison of CAF versus CMFP in metastatic breast cancer: Analysis of prognostic factors. J Clin Oncol 3:932-940, 1985

12. Coates A, Gebski V, Bishop JF, et al: Improving the quality of life during chemotherapy for advanced breast cancer: A comparison of intermittent and continuous treatment strategies. N Engl J Med 317:1490-1495, 1987

13. Aisner J, Weinberg V, Perloff M, et al: Chemotherapy vs chemoimmunotherapy (CAF v CAFVP v CMF each ± MER) for metastatic carcinoma of the breast: A CALGB study. J Clin Oncol 5:1523-1533, 1987

14. Creech RH, Catalano RB, Mastrangelo MJ, et al: An effective low-dose intermittent cyclophosphamide, methotrexate, and 5-fluorouracil treatment regimen for metastatic breast cancer. Cancer 35:1101-1107, 1975

15. Carbone PP, Bauer M, Band P, et al: Chemotherapy of disseminated breast cancer. Cancer 39:2916-2922, 1977

16. Tormey DC, Gelman R, Band PR, et al: Comparison of induction chemotherapies for metastatic breast cancer. Cancer 50:1235-1244, 1982

17. Henderson IC: Principles in the management of metastatic disease, in Harris JR, Hellman S, Henderson IC, et al (eds): Breast Diseases. Philadelphia, PA, Lippincott, 1992, pp 604-673

18. Bull JM, Tormey DC, Li S-H, et al: A randomized comparative trial of Adriamycin versus methotrexate in combination drug therapy. Cancer 41:1649-1657, 1978

19. Muss HB, White DR, Richards F II, et al: Adriamycin versus methotrexate in five-drug combination chemotherapy for advanced breast cancer. Cancer 42:2141-2148, 1978

20. Bezwoda WR, de Moor NG, Derman D, et al: Combination chemotherapy of metastatic breast cancer. Cancer 44:392-397, 1979

21. Tormey DC, Weinberg VE, Holland JF, et al: A randomized trial of five and three drug chemotherapy and chemoimmunotherapy in women with operable node positive breast cancer. J Clin Oncol 1:138-145, 1983

22. Brincker H, Rose C, von der Maase H, et al: A randomized study of CAF + TAM (tamoxifen) versus CMF + TAM in metastatic breast cancer. Proc Am Soc Clin Oncol 3:113, 1984 (abstr)

23. Tormey DC, Weinberg VE, Leone LA, et al: A comparison of intermittent vs continuous and of Adriamycin vs methotrexate 5-drug chemotherapy for advanced breast cancer. Am J Clin Oncol 7:231-239, 1984

24. Fossati R, Confalonieri C, Torri V, et al: Cytotoxic and hormonal treatment for metastatic breast cancer: A systematic review of published randomized trials involving 31,510 women. J Clin Oncol 16:3439-3460, 1998

25. Horwitz SB: Mechanism of action of Taxol. Trends Pharmacol Sci 13:134-136, 1992

26. Rao S, Horwitz SB, Ringel I: Direct photoaffinity labelling of tubulin with Taxol. J Natl Cancer Inst 84:785-788, 1992

27. Rowinsky EK, Burke PJ, Karp JE, et al: Phase I and pharmacodynamic study of Taxol in refractory acute leukemias. Cancer Res 49:4640-4647, 1989

28. Holmes FA, Walters RS, Theriault RL, et al: Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. J Natl Cancer Inst 83:1797-1805, 1991

29. O'Shaughnessy JA, Cowan KH: Current status of paclitaxel in the treatment of breast cancer. Breast Cancer Res Treat 33:27-37, 1995

30. Seidman AD, Reichman BS, Crown JPA, et al: Paclitaxel as second and subsequent therapy for metastatic breast cancer: Activity independent of prior anthracycline response. J Clin Oncol 13:1152-1159, 1995

31. Gianni L, Capri G, Munzone E, et al: Paclitaxel (Taxol) efficacy in patients with advanced breast cancer resistant to anthracyclines. Semin Oncol 21:29-33, 1994 (suppl 8)

32. Wilson WH, Berg SL, Bryant G, et al: Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: A phase I/II trial of 96-hour infusion. J Clin Oncol 12:1621-1629, 1994

33. Gelmon K, Nabholtz JM, Bontenbal M: Randomized trial of two doses of paclitaxel in metastatic breast cancer after failure of standard therapy. Ann Oncol 5:198-201, 1994 (suppl 5)

34. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. J Clin Oncol 12:2654-2666, 1994

35. Schiller JH, Storer B, Tutsch K, et al: A phase I trial of 3-hour infusions of paclitaxel (Taxol) with or without granulocyte colony-stimulating factor. Semin Oncol 21:9-14, 1994 (suppl 8)

36. Greco FA, Hainsworth JD: One-hour paclitaxel infusion schedules: A phase I/II comparative trial. Semin Oncol 22:118-123, 1995 (suppl 6)

37. Michael M, Bishop JF, Levi JA, et al: Australian multicentre phase II trial of paclitaxel in women with metastatic breast cancer and prior chemotherapy. Med J Aust 166:520-523, 1997

38. Rischin D, Webster LK, Millward MJ, et al: Cremophor pharmacokinetics in patients receiving 3-, 6- and 24-hour infusions of paclitaxel. J Natl Cancer Inst 88:1297-1301, 1996

39. Holmes FA, Valero V, Buzdar AU, et al: Final results: Randomized phase III trial of paclitaxel by 3 hour versus 96 hour infusion in patients (pt) with met breast cancer (MBC). Proc Am Soc Clin Oncol 17:110a, 1998 (abstr 426)

40. Holmes FA, Walters RS, Theriault RL, et al: Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. J Natl Cancer Inst 83:1797-1805, 1991

41. Reichman BS, Seidman AD, Crown JPA, et al: Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. J Clin Oncol 11:1943-1951, 1993

42. Nabholtz JM, Gelmon K, Bontenbal M, et al: Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858-1867, 1996

43. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treament. Cancer 47:207-214, 1981

44. Therapeutic Goods Administration: Guidelines for Good Clinical Research Practice (GCRP) in Australia. Canberra, Australia, Commonwealth Government Publisher, 1981

45. Spitzer WO, Dobson AJ, Hall J, et al: Measuring the quality of life of cancer patients: A concise QL-index for use by physicians. J Chron Dis 34:585-597, 1981

46. Matthews JNS, Altman DG, Campbell MJ, et al: Analysis of serial measurements in medical research. BMJ 300:230-235, 1990

47. Sledge GW, Robert N, Sparano JA, et al: Eastern Cooperative Oncology Group studies of paclitaxel and doxorubicin in advanced breast cancer. Semin Oncol 22:105-108, 1995 (suppl 6)

48. Sledge GW, Neuberg D, Ingle J, et al: Phase III trial of doxorubicin vs. paclitaxel vs. doxorubicin + paclitaxel as first-line therapy for metastatic breast cancer: An intergroup trial. Proc Am Soc Clin Oncol 16:1a, 1997 (abstr)

49. Gamucci T, Piccart M, Bruning P, et al: An EORTC crossover trial comparing single-agent Taxol and doxorubicin as first- and second-line chemotherapy in advanced breast cancer. Proc Am Soc Clin Oncol 16:154a, 1997 (abstr)

50. Gianni L, Munzone E, Capri G, et al: Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: High anti-tumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 13:2688-2699, 1995

51. Hortobagyi GN, Holmes FA: Optimal dosing of paclitaxel and doxorubicin in metastatic breast cancer. Semin Oncol 24:4-7, 1997 (suppl 3)

52. Gehl J, Boesgaard M, Paaske T, et al: Paclitaxel and doxorubicin in metastatic breast cancer. Semin Oncol 23:35-38, 1996 (suppl 15)

53. Bonadonna G, Zambetti M, Valagussa P: Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than 3 positive nodes: Ten year results. JAMA 273:542-547, 1995

54. Norton L, Simon R: The Norton-Simon hypothesis revisited. Cancer Treat Rep 70:163-169, 1986

55. Norton L: A Gompertzian model of human breast cancer growth. Cancer Res 48:7067-7071, 1988

56. Surbone A, Norton L: Kinetic concepts in the treatment of breast cancer. Ann NY Acad Sci 698:48-62, 1993

57. Hudis C, Seidman A, Raptis G, et al: Sequential adjuvant therapy: The Memorial Sloan-Kettering Cancer Center experience. Semin Oncol 23:58-64, 1996 (suppl 1)

58. Henderson IC, Berry D, Demetri G, et al: Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (pts) with node-positive primary breast cancer (BC). Proc Am Soc Clin Oncol 17:101a, 1998 (abstr 390A)