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Randomized Trial of Doxorubicin, Bisantrene, and Mitoxantrone in Advanced Breast Cancer: A Southwest Oncology Group Study

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Four hundred eleven women with metastatic breast cancer were randomly assigned to receive either 60 mg/m² doxorubicin (130 patients), 320 mg/m² bisantrene (146 patients), or 14 mg/m² mitoxantrone (135 patients). The doses were given intravenously every 3 weeks with a crossover design to determine their relative efficacy and toxicity. To be eligible, patients must have had one previous chemotherapy regimen, and patients who were estrogen receptor positive must have failed endocrine therapy. There were 365 patients assessable for response and 399 assessable for toxic effects. The median age was 57 years; 18% were premenopausal or perimenopausal. Visceral dominant disease was present in 66% of the patients. Ninety-seven percent of the patients had a disease-free interval from diagnosis to first recurrence of less than 1 year. The response rate was 28% with doxorubicin, 13% with bisantrene, and 14% with mitoxantrone (P = .004). Median time to treatment failure was 133 days with doxorubicin, 66 days with bisantrene, and 68 days with mitoxantrone (logrank P = .06). The median survival was 315 days for doxorubicin, 290 days for bisantrene, and 177 days for mitoxantrone (logrank P = .04), although survival at 2 years was similar for all three agents. There were five responses in the 66 patients crossed over to doxorubicin and one response each for patients crossed over to bisantrene (39 patients) or mitoxantrone (63 patients). Toxicity leading to discontinuance of therapy was more common with doxorubicin, and discontinuance of therapy was due primarily to patient's request or cardiotoxicity. The major dose-limiting toxic effect for all three agents was leukopenia. Nausea and vomiting, mucositis, and alopecia were more severe with doxorubicin. Congestive heart failure developed in nine patients treated with doxorubicin, zero patients treated with bisantrene, and two patients treated with mitoxantrone. A decrease in the left ventricular ejection fraction, as defined by moderate to severe Alexander grade changes, was more common in patients treated with doxorubicin (doxorubicin-treated patients = 20%, bisantrene-treated patients = 5%, and mitoxantrone-treated patients = 10%). This study demonstrates that bisantrene and mitoxantrone have only modest activity in metastatic breast carcinoma. The activity of doxorubicin is greater than that of the other two agents, but at a cost of increased toxicity. [J Natl Cancer Inst 83:1077–1084, 1991]

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Advances in the treatment of metastatic breast cancer with cytotoxic therapy have plateaued during the last 15 years (*1,2*). Twenty percent to 40% of patients will respond to single agents. Combination chemotherapy has been used, without dramatic success, in an attempt to improve treatment (*3-5*). Doxorubicin is reported to be the most active single agent in breast cancer, with a response rate as high as 50% (*6-9*). It is associated, however, with significant toxic effects including nausea and vomiting, myelosuppression, alopecia, and local skin ulceration with extravasation (*10*). Furthermore, the use of doxorubicin is limited due to cardiotoxicity noted with cumulative doses greater than 550 mg/m^2 (*11*). Clearly, these data indicate that there is a need for new agents with an improved therapeutic ratio.

Bisantrene is a new anthracene derivative which is thought to act as a nonspecific intercalator (*12*). It has activity in a number of animal tumor systems (*12*) and against human breast cancers tested in a human tumor cloning assay without total cross-resistance with doxorubicin (*13-15*). In addition, bisantrene has activity in phase II clinical trials of advanced breast cancer (*16-20*). Its major toxic effect is leukopenia, with a few patients having an anaphylactoid reaction, which seems to be prevented by dexamethasone premedication (*21*). Phlebitis is common, thus necessitating the use of a central venous catheter for chronic administration. Cardiotoxicity has not been observed with bisantrene.

Mitoxantrone (Novantrone; Lederle Laboratories, Wayne, N.J.) is a new bisaminoanthraquinone (*22*) which also has activity in animal tumor systems (*23-25*) and in human tumor cloning assays without total cross-resistance with doxorubicin (*14-27*). Phase II clinical trials demonstrate that this agent has activity in previously treated breast cancer patients (*28-32*). In addition, mitoxantrone is well tolerated, with leukopenia being the dose-limiting toxic effect. Alopecia, nausea, and vomiting are uncommon (*33,34*). Preclinical studies in the beagle-dog model (*35*) suggest that mitoxantrone is less cardiotoxic than doxorubicin. Cardiotoxicity, however, has been reported in patients treated with mitoxantrone (*36-39*). The relative cardiotoxicity of these two agents is not clearly defined.

This study is a randomized phase III trial designed to determine and compare the activity and toxicity of doxorubicin, bisantrene, and mitoxantrone as cytotoxic agents administered to previously treated patients with metastatic breast cancer.

Patients and Methods

Patients

Patients were required to have adenocarcinoma of the breast with objectively measurable or evaluable noncentral nervous system metastasis. Patients were also required to have a performance status (Southwest Oncology Group) of 0-2, a white blood cell count of more than 4000/μL, a platelet count of more than 125 000/μL (unless lower blood cell counts were due to bone marrow involvement by tumor), a creatinine level of less than 2.0 mg/dL, and a total bilirubin level of less than 2.0 mg/dL. Patients with a history of congestive heart failure, a myocardial infarction within 6 months, or severe angina pectoris were not eligible. A normal left ventricular ejection fraction (LVEF), as measured by radionuclide cardioangiography or echocardiography, was required. In addition, patients were required to have been treated with one prior chemotherapeutic regimen for metastatic disease or with adjuvant therapy (not including doxorubicin, bisantrene, or mitoxantrone). Estrogen receptor-positive patients must have failed an endocrine therapy unless they had lymphangitic lung metastasis or advanced liver involvement. Prior radiation therapy, if done, must not have included more than 10% of the bone marrow. Concurrent palliative radiation therapy to the nonindex bone lesions was allowed. Concomitant chemotherapy, hormonal therapy, or immunotherapy was not allowed. All patients gave informed consent.

Randomization

Patients were randomly assigned by the Southwest Oncology Group Statistical Center. Patients having progressive disease on their initial treatment were offered reassignment to one of the two remaining agents, if they continued to meet initial eligibility requirements.

Treatment

Patients received one of the three following treatments: 1) doxorubicin at 60 mg/m^2 given intravenously (IV) for 15 minutes, 2) bisantrene at 320 mg/m^2 given IV for 2 hours (after the first 45 patients, the protocol was modified to change the starting dose of bisantrene from 260 mg/m^2 to 320 mg/m^2 in an attempt to obtain myelosuppression equivalent to the other two agents), or 3) mitoxantrone at 14 mg/m^2 given IV for 10 minutes. Drug administration was repeated every 3 weeks, if toxicity permitted. Patients receiving bisantrene were premedicated with 4 mg of dexamethasone orally the night before, the morning of, and the day following treatment. Just prior to bisantrene infusion, 50 mg of diphenhydramine hydrochloride was administered IV in an attempt to avoid anaphylactoid reactions. Placement of a central venous catheter was encouraged in patients treated with bisantrene.

Drug doses were modified (decreased or escalated) to obtain a white blood cell count nadir of 1000-2000/μL and/or a platelet count nadir of 50 000-99 000/μL. Doses were decreased by one dose level for grade III or greater nonhematologic and noncardiac toxic effects. Doxorubicin was continued in patients with stable disease, partial remission, or complete remission beyond a total dose of 550 mg/m^2 if the cardiac function remained normal, as determined by physical examination and LVEF measured prior to each course.

Evaluation

Prior to therapy, all patients underwent evaluation that included history, physical examination, performance status determination, electrocardiogram, complete blood cell count with platelet count, renal and liver function tests, measurement of LVEF, and chest x ray. Other x rays and radiologic scans were also obtained as clinically indicated. A complete blood cell count nadir with platelet count was obtained 9-14 days after therapy. Follow-up x-ray scans for response measurements, renal and liver function tests, and follow-up LVEF measurement were obtained every 9 weeks. LVEF measurement was also ob-

tained prior to each cycle of therapy in patients treated with greater than or equal to 550 mg/m^2 doxorubicin.

Outcome Criteria

Standard Southwest Oncology Group response criteria were used. Complete response required disappearance of all known disease for at least 4 weeks. For patients with bone-only disease, a complete response required all lytic lesions to be remineralized, all bone pain resolved (off pain medication), and no new bone lesions as determined by radiologic study. Partial response required a greater than 50% decrease in tumor size (using the sum of the products of perpendicular diameters) for at least 4 weeks. In patients with bone-only disease, a partial response required disappearance of bone pain and a decrease in the size and density of bone lesions, as determined by radiographic studies, for at least 6 weeks. Stable disease required no significant change for at least 6 weeks. Increasing disease required appearance of a new metastatic lesion, a greater than 25% increase in existing lesions, or reappearance of an old lesion in a patient in complete remission. Institutional investigators coded responses and toxicity. These response and toxicity measurements were reviewed and verified by J. D. Cowan and J. Neidhart in a blinded procedure for patient's name, treatment arm, and institution.

Response duration was measured from the first documentation of response to the first documentation of progression. The time to treatment failure was defined as the time from randomization to the time of first documentation of disease progression on treatment, death on treatment, or death off treatment due to toxic effects or treatment refusal. Reaching the maximum dose of doxorubicin was not considered a failure. Survival was measured from the time of randomization to death.

Statistical Methods

Categorical outcomes were compared using chi-square tests. The percentage of patients responding (complete response or partial response), the percentage of patients experiencing severe or worse hematologic toxic effects, and the distributions of worst grade of nonhematologic toxic effects (none/mild, moderate, severe, or worse) were compared on the three treatment arms.

For time-to-event variables (survival or time to treatment failure), Kaplan and Meier estimation (*40*), logrank tests (*41*), and Cox modeling (*42*) were used. Patients off treatment due to maximum cumulative doxorubicin dose or for reasons unrelated to disease were censored for time to treatment failure analysis at time off treatment.

Results

Patient Characteristics

A total of 411 patients were randomly assigned to treatment from January 1983 to October 1986. Forty-six (11%) were found to be ineligible. The most frequent reason for ineligibility related to the extent of prior therapy (either more than one prior regimen for metastatic disease or no prior therapy). All eligible patients were included for analysis of efficacy and survival.

Patient characteristics are summarized in Table 1. The treatment arms were reasonably well balanced with respect to age, menopausal status, performance status, dominant disease site, number of disease sites, measurability of disease, initial LVEF, and prior chemotherapy. Imbalances were observed in receptor status, number of prior hormone therapies, and disease-free interval. Fewer patients on the doxorubicin treatment arm were estrogen receptor negative, more had been previously treated with one or more endocrine therapies, and fewer had metastatic disease at diagnosis.

Table 1. Demographic and clinical features

Patient characteristic	Treatment group*		
	Doxorubicin (N=117)	Bisantrene (N=128)	Mitoxantrone (N=120)
Age, y			
Median	56	57	56
Range	22-82	28-79	29-79
% >60 y	35	42	38
Premenopausal or perimenopausal	22 (19)	25 (20)	20 (17)
Southwest Oncology Group performance status			
0	31 (26)	29 (23)	30 (25)
1	56 (48)	62 (48)	58 (48)
2	30 (26)	37 (29)	32 (27)
Estrogen receptor			
Positive	54 (46)	43 (34)	48 (40)
Negative	44 (38)	75 (58)	56 (47)
Unknown	19 (16)	10 (8)	16 (13)
Dominant disease site			
Bone	27 (23)	38 (30)	31 (26)
Soft tissue	7 (6)	13 (10)	8 (7)
Visceral	83 (71)	77 (60)	81 (67)
No. of disease sites			
1	46 (39)	46 (36)	41 (34)
2	38 (33)	55 (43)	53 (44)
3	26 (22)	20 (16)	22 (19)
4	7 (6)	7 (5)	4 (3)
Measurable disease	86 (74)	103 (80)	102 (85)
Initial LVEF			
Median	65	63	64
Range	49-86	45-97	46-88
Prior chemotherapy			
Adjuvant chemotherapy—recurrence >6 mo after therapy	24 (21)	24 (19)	19 (16)
Adjuvant chemotherapy—recurrence <6 mo after therapy	14 (12)	19 (15)	30 (25)
Therapy for metastases	79 (67)	85 (66)	71 (59)
Prior hormone therapy			
None	41 (35)	67 (52)	54 (45)
1 regimen	49 (42)	41 (32)	36 (30)
>1 regimen	27 (23)	20 (16)	30 (25)
Disease-free interval			
0†	31 (26)	57 (45)	48 (40)
1 mo-1 y	85 (73)	68 (53)	65 (54)
>1 y	1 (1)	3 (2)	7 (5)

*Unless otherwise specified, values = No. of patients (%).
†0 = metastastic disease at initial presentation.

Response to Therapy

Pre-crossover response data are summarized in Table 2. Complete responses were rare in all three treatment arms. Doxorubicin demonstrated a higher response rate (P = .004). Response was not related to measurability status (bidimensionally measurable or not) or to dominant disease site (visceral or not). Raising the starting dose of bisantrene to 320 mg/m^2 was not associated with improved response. The median durations of response were 263 days for doxorubicin, 126 days for bisantrene, and 301 days for mitoxantrone.

Among 117 eligible patients on the doxorubicin treatment arm, treatment failure was due to disease progression or death in 65, toxicity in 24, and treatment-related refusal in 17. Of the remaining 11 patients, two went off treatment for reasons unrelated to disease progression or treatment, and nine discontinued treatment because the maximum doxorubicin dosage had been reached. Among 128 eligible bisantrene-treated patients, 115 had disease progression or died on treatment, seven went off treatment due to toxic effects, five refused further treatment, and one went off treatment due to unrelated reasons. Finally, among the 120 eligible patients treated with mitoxantrone, 106 had disease progression or died on treatment, nine went off treatment due to toxic effects, two refused further treatment, and three went off treatment due to unrelated reasons. There was a borderline significant (P = .06 by three-sample log test) time-to-treatment-failure advantage for doxorubicin (Fig. 1). The median time to treatment failure was 133 days for doxorubicin, 66 days for bisantrene, and 68 days for mitoxantrone.

One hundred sixty-eight patients underwent crossover randomization at the time of disease progression on the initial treatment arm (Table 2). Five patients responded to doxorubicin, and one each responded to bisantrene and mitoxantrone.

Survival

Survival in the three treatment arms was significantly different (three-sample logrank, P = .04) (Fig. 2). Patients treated with doxorubicin or bisantrene survived longer than patients treated with mitoxantrone. The median survival for doxorubicin was 315 days; for bisantrene, 290 days; and for mitoxantrone, 177 days. The estimated 2-year survival was low in all three treatment arms (9% for doxorubicin and mitoxantrone and 11% for bisantrene). Survival after crossover was poor on all three agents (median, 63-77 days).

Table 2. Pre-crossover best response rates for all eligible patients

	No. of patients in treatment group (%)		
	Doxorubicin	Bisantrene	Mitoxantrone
Pre-crossover patients			
Eligible patients	117	128	120
Complete responders	1 (1)	2 (2)	1 (1)
Partial responders	32 (27)	15 (12)	16 (13)
Total responders*	33 (28)	17 (13)	17 (14)
Post-crossover patients			
Eligible patients	66	39	63
Total responders	5 (8)	1 (3)	1 (2)
Pre-crossover responder	1	0	0

*P = .004.

The stepwise Cox proportional hazards model procedure was used to test for patient characteristics associated with survival. The variables tested included performance status, estrogen receptor status, dominant disease status, number of metastatic sites, presence of measurable disease, menopausal status, age, obesity, initial LVEF, disease progression or recurrence while on prior chemotherapy versus recurrence more than 6 months after completion of adjuvant chemotherapy, initial aspartate aminotransferase levels, number of prior hormonal therapies, and treatment arm. Characteristics related to decreased survival were elevated aspartate aminotransferase levels, estrogen receptor-negative disease, fewer than two prior hormonal therapies, performance status of 2, and premenopausal or perimenopausal status. After adjustment for these variables, survival time in the mitoxantrone treatment arm was still shorter than in the doxorubicin and bisantrene treatment arms. The estimated mitoxantrone-to-doxorubicin and bisantrene-to-doxorubicin hazard ratios were 1.48 (95% confidence interval [CI] = 1.12-1.95) and 0.92 (95% CI = 0.7-1.21), respectively.

Toxicity

Myelosuppression was the most frequent toxic effect and, as intended in the protocol design, was similar for all three agents (Table 3). Over 70% of patients on all treatment arms developed a white blood cell count nadir of less than 2000/μL (chi-square, 2 degrees of freedom, P = .10). The proportion of patients with a white blood cell count nadir below 1000/μL was highest with mitoxantrone. Neutropenic fever developed in five patients treated with doxorubicin, six with bisantrene, and nine with mitoxantrone. Thrombocytopenia was less severe than leukopenia, but did lead to discontinuation of treatment in one patient after eight cycles of mitoxantrone.

The nonhematologic and noncardiac toxic effects occurring in at least 10% of patients are also presented in Table 3. Nausea and vomiting (P = .02) and mucositis (P<.0001) were experienced more commonly in patients treated with doxorubicin. Phlebitis was more common in patients treated with bisantrene (P = .02). Alopecia occurred in all treatment groups, but was more common and more severe in patients treated with doxorubicin (P<.0001). Finally, hypotension (even with medication) was not an infrequent toxic effect of bisantrene (P<.0001). Seven patients (5%) developed symptomatic hypotension requiring treatment with IV fluids. Two patients required discontinuance of therapy with bisantrene because of hypotension. Cardiotoxicity was evaluated by clinical assessment and measurement of LVEF. Congestive heart failure developed in 7% of doxorubicin-treated patients, the majority after seven cycles of therapy (Table 4). Congestive heart failure was not seen with bisantrene, and it occurred in only two patients treated with mitoxantrone (one at 10 and one at 18 courses).

LVEF data using the Alexander grading system (*43*) are presented in Table 5. These LVEF data are subject to bias. First, LVEF measurements were taken more often on doxorubicin-treated patients; measurements were required prior to each dose of doxorubicin after reaching a total dose of 550 mg/m^2 (rather than measuring the LVEF every 9 weeks), and patients remained on treatment longer with doxorubicin. This situation would tend to make doxorubicin look worse than the other two

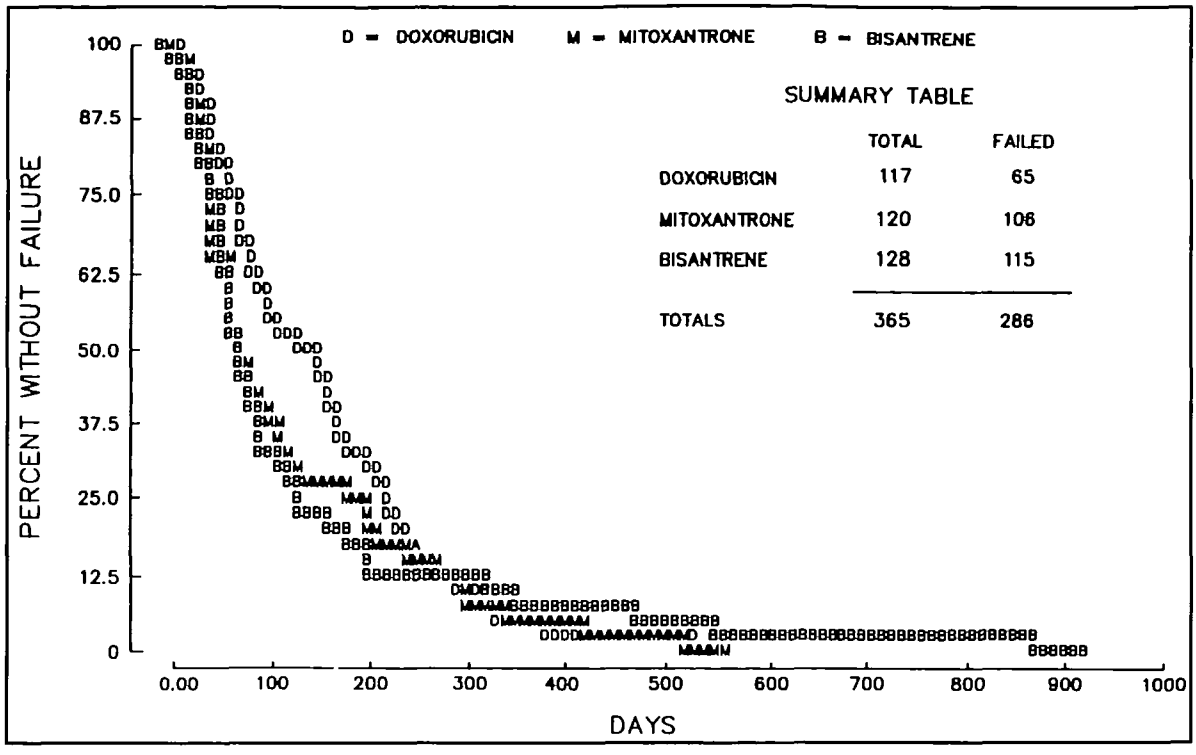

Fig. 1. Time to treatment failure. Cumulative proportion of all eligible patients failure-free as a function of time.

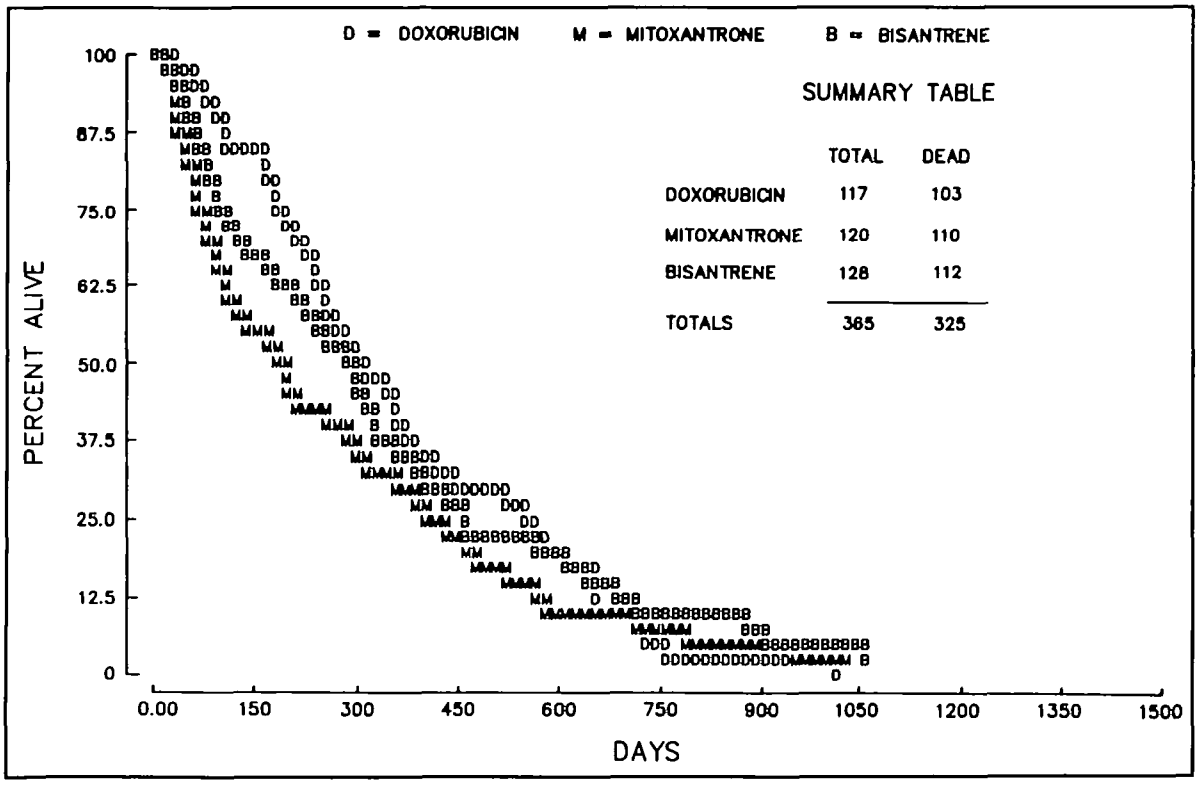

Fig. 2. Survival. Cumulative proportion of all eligible patients surviving.

agents. Keeping these potential biases in mind, Alexander moderate and severe grade changes developed in 20% of doxorubicin-treated patients, but in only 5% of bisantrene-treated patients and in only 10% of mitoxantrone-treated patients. Moderate to severe grade changes were uncommon with all three agents through seven cycles of treatment. After eight or more cycles of therapy, 41% of doxorubicin-treated patients developed moderate to severe Alexander grade changes, while this occurred in less than 20% of bisantrene- or mitoxantrone-treated patients.

Discussion

This study was developed to evaluate the relative activity and toxicity of doxorubicin, bisantrene, and mitoxantrone in previously treated patients with metastatic breast cancer. Single-

Table 3. Noncardiac toxic effects

Toxic effect	% of patients		
	Doxorubicin	Bisantrene	Mitoxantrone
Nausea and vomiting*			
None	27	52	46
Mild	24	17	20
Moderate	35	22	20
Severe	13	9	14
Mucositis*			
None	66	90	93
Mild	11	4	2
Moderate	14	4	3
Severe	9	2	2
Phlebitis*			
None	89	82	96
Mild	5	7	1
Moderate	5	7	1
Severe	1	4	1
Alopecia*			
None	19	70	70
Mild	7	13	15
Moderate	13	9	8
Severe	61	7	7
Hypotension*			
None	99	71	99
Mild	<1	12	<1
Moderate	0	12	0
Severe	0	5	0
White blood cell count nadir, cells/μL			
<2000	76	72	81
<1000	27	22	36
Platelete count nadir, cells/μL			
<50 000	14	2	16
<25 000	5	1	6

*Tallied by most severe occurrence for each patient.

Table 4. Cardiac toxic effects

	Treatment group		
	Doxorubicin	Bisantrene	Mitoxantrone
1-7 courses			
No. of patients	128	138	133
Average No. of courses	5	4	4
No. of patients with CHF* (%)	2 (2)	0	0
>7 courses			
No. of patients	42	25	35
Average no. of courses	10	17	11
No. of patients with CHF* (%)	7 (17)	0	2 (6)
All courses			
No. of patients	128	138	133
Average No. of courses	6	5	5
No. of patients with CHF* (%)	9 (7)	0	2 (2)

*CHF = congestive heart failure.

Table 5. Cardiotoxicity by LVEF grade*

	Treatment group		
	Doxorubicin	Bisantrene	Mitoxantrone
No. of patients treated	128	138	133
No. of patients with baseline and follow-up LVEF	83	76	71
Worst grade LVEF for each patient as %			
Mild	39	29	37
Moderate	18	5	10
Severe	2	0	0
Courses 1-3			
No. of patients with baseline and follow-up LVEF	63	60	55
% of patients with moderate or severe grade LVEF	3	0	2
Courses 4-7			
No. of patients with baseline and follow-up LVEF	56	37	40
% of patients with moderate or severe grade LVEF	9	3	5
Courses >7			
No. of patients with baseline and follow-up LVEF	29	16	24
% of patients with moderate or severe grade LVEF	41	13	17

*Grade: mild = >10% decrease from baseline LVEF. Moderate = >15% decrease from baseline LVEF and follow-up LVEF <45%. Severe = LVEF <30% and congestive heart failure (*43*).

agent doxorubicin was chosen as the standard agent for comparison in this trial because it is reportedly the most active single agent in breast cancer (*6-9*). Bisantrene and mitoxantrone were chosen because of their structural similarity to doxorubicin (*12,23*), because of their preclinical activity in a variety of tumor models (*12,15,23-25,27*), and because of their activity with modest toxicity in phase II breast cancer trials (*16-20,28-32*). A crossover design was used to determine the level of cross-resistance among the agents.

The study demonstrates that doxorubicin is more active than bisantrene or mitoxantrone in this patient population. The pre-crossover response rate of all eligible patients was 28% for doxorubicin, which is similar to that of other studies (*6-9,41*). This response rate was superior to the response rate for both bisantrene and mitoxantrone. The time to treatment failure was also longer with doxorubicin. Overall survival of patients was similar for doxorubicin and bisantrene, both of which were superior to mitoxantrone. Even after controlling for various other clinical factors in a multivariate analysis, mitoxantrone remained inferior. However, there was no long-term benefit to any treatment arm.

Although patients treated with doxorubicin demonstrated a superior response rate and time to treatment failure, toxicity was also greater with this agent. Myelotoxicity was similar for the three agents, but nonhematologic toxicity was more severe with doxorubicin. Furthermore, patients on doxorubicin requested to stop therapy more often than patients treated with bisantrene or mitoxantrone. Nausea and vomiting, mucositis, and alopecia were all more common with doxorubicin therapy and probably played a role in patients' requests to discontinue treatment.

Cardiotoxicity was also more frequent with doxorubicin and was the most common toxic effect leading to discontinuation of therapy for all three agents. Cardiotoxicity occurred in 23% of doxorubicin-treated patients, 4% of bisantrene-treated patients, and 12% of patients treated with mitoxantrone. Clinical congestive heart failure or a decrease in LVEF developed much more frequently in patients treated with doxorubicin than in patients treated with bisantrene or mitoxantrone. It should be emphasized, however, that the study design called for continuation of doxorubicin therapy in responding patients beyond a total dose of 550 mg/m^2 together with careful cardiac monitoring. This design may account in part for the high incidence of cardiotoxicity in this trial.

Cross-resistance among the three agents in the dosage and schedule used in this study was marked. Patients rarely responded to any of the agents, although responses were slightly more frequent with doxorubicin. Thus, patients failing to respond to doxorubicin as initial therapy are unlikely to respond to salvage treatment with bisantrene or mitoxantrone. There are no other large, randomized comparisons of doxorubicin with bisantrene in metastatic breast cancer. However, there have been two other reports comparing doxorubicin with mitoxantrone. Neidhart et al. (*32*) reported a single-institution randomized trial of 90 women with metastatic breast cancer treated with either doxorubicin at 60 mg/m^2 or mitoxantrone at 12 mg/m^2 every 3 weeks, with a crossover design. More recently, Henderson et al. (*44*) reported a large multi-institutional trial which randomly assigned a total of 325 women with metastatic breast cancer to either 75 mg/m^2 doxorubicin or 14 mg/m^2 mitoxantrone every 3 weeks (also with a crossover design). The patient characteristics in these two studies were similar to those in our study in most respects, although our patients exhibited more adverse prognostic factors. First, neither of the other studies required prior hormonal therapy in estrogen receptor-positive patients. Second, visceral metastases were present in 66% of our patients, but in only 40%-49% of patients in the other two studies. Finally, the disease-free interval from diagnosis to first recurrence was significantly shorter in the present study.

Nevertheless, the efficacy data for the three studies are similar. The response rate for doxorubicin ranged between 28% and 30%, consistently higher than that for mitoxantrone (14%-21%). Time-to-treatment-failure differences also favored doxorubicin in all three studies. All three studies demonstrated only occasional crossover responses to each agent. Survival data were not reported in the study by Neidhart et al. (*32*), but the study by Henderson et al. (*44*) showed no difference in survival times of patients between doxorubicin and mitoxantrone (median of 268 days and 273 days, respectively). This is at variance with our data showing a median survival time of 315 days with doxorubicin and 177 days for mitoxantrone. The reason for shorter survival time for mitoxantrone in the present study is not clear. It might, however, relate to a difference in our patient population (i.e., more visceral disease or shorter disease-free interval from diagnosis) or to imbalances in patient characteristics in the present study (i.e., more estrogen receptor-positive patients in the doxorubicin treatment arm). In addition, this finding raises the possibility that patients with these poor risk factors may be the ones who benefit most from initial doxorubicin therapy.

Toxicity data from the studies by Neidhart et al. (*32*) and Henderson et al. (*44*) are also similar to those of the present study. Nonhematologic toxic effects, including nausea and vomiting, mucositis, alopecia, and cardiotoxicity, were more severe with doxorubicin.

In summary, this study demonstrates that in a patient population with a high proportion of visceral metastases and a short disease-free interval from diagnosis, doxorubicin provides a higher response rate, longer time to treatment failure, and longer survival time than mitoxantrone. The response rate and time to treatment failure for doxorubicin are also superior to those for bisantrene, although the survival time is similar.

An important question is whether bisantrene or mitoxantrone has sufficient activity in our study to warrant further evaluation. By the criteria discussed by Fleming (*45*) for treatment evaluation in active control studies, our study suggests that bisantrene is sufficiently active. Assuming doxorubicin improves survival time over no treatment by about 25%, and considering the similarity of survival times on the bisantrene and doxorubicin treatment arms, it can be concluded that bisantrene also improves survival time over no treatment. The same argument does not hold for mitoxantrone in our study, since survival time for patients on mitoxantrone is estimated to be worse than that for patients on doxorubicin. Our study does not support the use of mitoxantrone as a single agent in this population of advanced breast cancer patients.

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