A Comparison of Mitoxantrone and Doxorubicin in Breast Cancer

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Ninety patients with breast cancer refractory to cyclophosphamide/fluorouracil/methotrexate (CMF) have been randomized in their treatment, receiving either doxorubicin or mitoxantrone. Seventy-nine have received two full courses of therapy. Twelve of the 40 (30%) who initially received doxorubicin responded, whereas eight of the 47 (17%) who received mitoxantrone responded. These rates are not statistically different. The degree of myelosuppression was equivalent. Patients who received mitoxantrone had less nausea, vomiting, alopecia, and fatique. Controllable clinical congestive heart failure developed in seven patients, and four others had a deterioration of noninvasive measures of cardiac function without clinical failure. One patient with clinical heart failure developing received only doxorubicin and one, only mitoxantrone, whereas the others received both agents. The duration of remission and time lapsed before disease progression were almost identical for the two regimens. This study included a crossover design. Two of 22 (10%) patients receiving doxorubicin and five of 24 (21%) receiving mitoxantrone as secondary therapy responded. This suggests that there is not absolute cross-resistance between these agents. We conclude that the efficacy of these two drugs is comparable in patients refractory to CMF, though the nonhematologic side effects of mitoxantrone are less.
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MAJOR ADVANCES in breast cancer throughout the past decade have included the widespread introduction of combination and multimodality treatments and the development of new agents such as doxorubicin and tamoxifen. Patients presenting with symptomatic disease can now obtain substantial relief through first-line chemotherapy, and some patients probably live longer as a result of treatment. Advanced breast cancer, however, is not curable,[1,2] and survival is inadequate in terms of both quality and duration.[3–5] The therapies presently available for patients for whom first-line therapy has failed offer minimal, if any, clinical benefits. There is clearly a need for new approaches and new agents for therapy for this disease.

Several bis-substituted anthraquinones were introduced into clinical trials about 5 years ago as an entirely new class of anticancer agents. Dihydroxyanthracenedione (mitoxantrone) has emerged as the most promising of this group of agents. In 1980, we initiated a prospective comparison of the most active standard agent for breast cancer, doxorubicin, and mitoxantrone as therapy for minimally pretreated patients with breast cancer. Early results of that study were published 2 years ago both in abstract form and in a preliminary manuscript.[6,7] This is the final report of that study.

PATIENTS AND METHODS

Women with metastatic or unresectable regional breast cancer were eligible for this study if they had received no more than one prior chemotherapy regimen, they had not received anthracyclines, and their previous therapy had failed. Patients were required to be ambulatory for at least half a waking day (scoring from 0 to 2 on the Zubrod Activity Scale), though patients who had a greater restriction of activity owing to bone pain alone were permitted if they could otherwise be up and about. Patients must have had measurable or evaluable disease. Patients with liver and renal dysfunction were not excluded. All patients granted written consent after being informed of the experimental nature of the therapies. They were then randomized to receive either doxorubicin (60 mg/m^2) or mitoxantrone (12 mg/m^2) as initial treatment. Patients with compromised bone marrow reserve (WBC count $< 3000/\mu L$ or platelets $< 100{,}000/\mu L$) received an initial dose that was reduced by 25%. Doses were repeated every 3 weeks and increased by 25% until the patient achieved a WBC nadir of $\leq 2{,}500/\mu L$. Patients with prolonged or life-threatening marrow suppression or severe nonhematologic toxicity (World Health Organization grade 3 or 4[8]) had

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their dose reduced by 25% to 50%. A crossover design was also used: patients who experienced disease progression after two courses or those who failed to respond to four courses received the alternate regimen. Mitoxantrone was initially supplied by the Investigational Drug Branch of the CTEP, National Cancer Institute, and later by the American Cyanamid Company, Pearl River, NY. Patients were interviewed by a research nurse and their physician before each therapy, and any interim effects possibly related to therapy were recorded as toxicities. Increasing shortness of breath in the presence of a changing and abnormal gated acquisition (MUGA) scan (< 0.50) or systolic time interval (STI) measurements ($\Delta D \leq 28\%$) or a physician's clinical diagnosis of probable congestive heart failure (CHF) were designated as drug-related CHF. Either MUGA scans or STI measurements were scheduled before therapy, at least every three courses, and at crossover. Complete blood counts were obtained weekly.

Patients were considered evaluable for response if they completed two courses of therapy or showed documented disease progression at any time. Complete response was defined as the disappearance of all evidence of disease for at least one course of therapy. Partial response required a 50% decrease in all lesions that persisted for at least one full course of therapy. Complete relief of pain in the absence of analgesics for at least 4 weeks was accepted as a partial response if the pain was clearly cancer related and had initially required analgesic therapy for relief. Coombes et al have shown good correlation between relief of bone pain in patients with breast cancer and response in nonosseous sites using standard Union Internationale Contre le Cancer (UICC) criteria.[9] We have chosen to use pain as a response end point since palliation is an important goal in this setting and the randomized design helps alleviate bias that might result from using subjective end points. We have chosen more stringent criteria for pain relief than those used by Coombes et al and require complete and durable relief of pain before designation of a response. The duration of response was calculated from the date of the initial response. Effusions, inflammatory skin lesions, sclerotic bone lesions, and laboratory abnormalities were not accepted as evaluable lesions. Response determinations were initially made by the patient's physician and a research nurse. They were then confirmed by at least one of the investigators in a blinded review of response data. The statistical analysis of frequency data relied on Yate's corrected chi-square test or Fisher's exact test when the total number of observations was ≤ 20.

RESULTS

Patient characteristics are presented in Table 1. Ninety patients entered the study. Two patients were entered on the mitoxantrone arm and one on doxorubicin without measurable disease

Table 1. Patient Characteristics

Characteristics	Initial Therapy	
	Doxorubicin (n)	Mitoxantrone (n)
Number of patients registered	41	49
Eligible patients	40	47
Age: median (range)	61 (32–79)	57 (35–77)
Zubrod performance status		
0	18	15
1	10	21
2	9	8
3	3	3
Unknown	1	2
Prior therapy		
None	3	1
Chemotherapy (CMF + tamoxifen)	18	25
Chemotherapy and radiation	20	23
Number of metastatic sites		
1	16	22
2	19	17
3	5	6
4–5	1	4
Mean	1.8	1.9
Sites of metastases		
Bone	24	31
Lung	12	15
Skin or soft tissue	13	15
Lymph node	9	8
Liver	8	8
Breast	1	4
Months from diagnosis to entry		
Mean	66.8	63.7

Table 2. Responses

Initial Therapy	Doxorubicin No. of Patients	Doxorubicin Percentage Responding	Doxorubicin 95% Confidence Interval	Mitoxantrone No. of Patients	Mitoxantrone Percentage Responding	Mitoxantrone 95% Confidence Interval
All eligible patients						
Total	40			47		
Complete response	1	30	16–44	1	17	6–28
Partial response	11			7		
Patients receiving two full courses						
Total	39			40		
Complete response	1	33	19–48	1	23	10–35
Partial response	11			7		
Secondary therapy						
Total	22			24		
Complete response	1	10	0–20	0	21	5–37
Partial response	1			5		

and were therefore not eligible. It is too early to evaluate one patient receiving initial mitoxantrone, and two patients chose not to return after the first course although neither had serious toxicity or subjective disease progression. Four patients receiving mitoxantrone and one receiving doxorubicin failed to complete two courses because of disease progression or toxicity. These patients have however been designated as having progressive disease. Thirty-nine patients initially treated with doxorubicin and 40 initially treated with mitoxantrone therefore received two full courses of therapy. Response rates are reported for all eligible patients and for patients completing two full courses of therapy. All patients were evaluable for nonhematologic toxicity. Courses were evaluable for hematologic toxicity if weekly interim blood counts were obtained. The initial performance status was near normal (Zubrod 0 to 1) in about 75% of the patients. Three patients had refused standard regimens for breast cancer and entered this study without prior therapy. Patients were equally distributed between the two arms by performance status, interval from diagnosis to treatment, types of prior treatment, responses to prior treatment, sites of metastases, and number of metastatic sites.

Table 2 shows the patient response to both primary treatment and secondary treatment (after crossover). The response rate to primary treatment for all eligible patients was 30% with doxorubicin and 17% with mitoxantrone. One patient had a complete response to each agent. The 95% confidence intervals overlapped, and the differences were not statistically significant ($P < .2$). If only patients who received two full courses of therapy are considered, the response rates to mitoxantrone and doxorubicin are 23% and 33%, respectively. Seven of 46 patients who received either agent as secondary therapy (after crossover) had a response. Again the response

Table 3. Sites of Response

Site	Doxorubicin	Mitoxantrone
Soft tissue	9	8
Bone		
Pain	7	5
Scan	1	2
X-rays	3	2
Lung	3	1
Liver	1	1

Table 4. Response Duration and Time to Progression

	Doxorubicin	Mitoxantrone
Response durations (median days)		
Initial therapy		
Complete response	210	127+
Partial response	91	116
Secondary therapy		
Complete response	91	—
Partial response	141	189
Time to progression		
Initial therapy	134	109
Secondary therapy	135	110
Overall	135	109

Table 5. Hematologic Toxicity for Primary Treatment

Initial Treatment	No. of Patients	Evaluable Course	WBC × $10^3/\mu L$ Nadir (Range)	Platelets × $10^3/\mu L$ Nadir (Range)
Doxorubicin	40	184	2.6 (0.6–11.1)	185 (16–469)
Mitoxantrone	47	180	2.1 (1.5–10.7)	157 (14–529)

rates (mitoxantrone, 21%; doxorubicin, 10%) were not significantly different for the two agents. Overall response rates (primary and secondary treatment) are the same (22% *v* 25%). The response sites are shown in Table 3; they were similar for both agents. Responses were seen within two courses for most patients, although two patients on each regimen received four or five courses before a response was noted. Pain relief was the sole criterion of response for three patients receiving doxorubicin and one receiving mitoxantrone. Response durations and time to progression are presented in Table 4 and are also similar. Responses lasted for about 3 months in most patients but continued for more than a year in some.

Table 5 shows that the hematologic toxicity of these drugs was not notably different. More patients treated with mitoxantrone (17%) required an escalation of the dose to achieve the desired level of myelosuppression than did patients treated with doxorubicin (8%). Table 6 shows the frequency and median grade of the more common, nonhematologic toxic reactions. Nausea and vomiting ($P < .001$), alopecia ($P < .001$), and fatigue ($P < .05$) occurred less frequently as a result of treatment with mitoxantrone and tended to be less severe. Symptoms suggestive of CHF developed in seven patients, and four others experienced a deterioration in cardiac function by noninvasive measurements without clinical failure (Table 7). In all cases, failure was easily controlled or required no therapy.

DISCUSSION

This study was designed to determine comparative response rates, response durations, and side effects of mitoxantrone and doxorubicin in patients with breast cancer who had failed therapy with CMF. Doxorubicin was chosen because it is the most active standard agent in breast cancer. The complete and partial response rates to these agents are similar, and observed differences are not statistically significant. Time to progression and the duration of remissions were almost identical for these agents in both primary and secondary treatment. However, if tested on a sufficient number of patients, there is a trend favoring doxorubicin that may prove significant. If all eligible patients in our study were considered in the analysis of patient response, the trend would favor doxorubicin (17% *v* 30%), but the difference is still not significant ($P = .17$).

We are aware of no other reported direct comparative study of these two agents, though two larger studies are presently being conducted by the Southwest Oncology Group and the Lederle Collaborative Study Group. Still the responses seen in our study are consistent with findings reported by others. Yap and colleagues[10] reported a 22% overall response rate in 31 patients with highly refractive breast cancer who were treated with mitoxantrone at a dosage of 4 $mg/m^2/d$ for 5 consecutive days each month. Smyth and colleagues treated 134 breast cancer patients with mitoxantrone at 17 mg/m^2 once every 3 weeks as primary therapy.[11] Their response rate was 35%, including six patients showing a complete response. Their regimen was similar to ours, but they used a slightly higher starting dose. The Eastern Cooperative group used a dosage of 4 $mg/m^2/d$ for 3 days every 3 weeks on patients for whom one prior chemotherapy regimen[12] had failed; they have observed only two partial responses in 34 patients (6%). Mitoxantrone has shown reproducible but modest efficacy as a sin-

Table 6. Percentage and Median Grade of More Common Toxicities

	Doxorubicin (Median Grade)	Mitoxantrone (Median Grade)
Nausea and vomiting	77% (2.5)	48% (1.5)
Alopecia*	90% (3)	33% (1)
Fatigue	36% (1.5)	20% (1)
Diarrhea	6% (1)	2% (1)
Anorexia	6% (1)	6% (1)
Stomatitis	6% (1.5)	5% (2)

*Alopecia for first treatment regimen only.

Table 7. Cardiotoxicity

Patient	Chest Irradiation	Doxorubicin, Total mg/m^2	Mitoxantrone, Total mg/m^2	Evidence for Cardiotoxicity
1	no	270	45	STI
11	no	394	86	STI; MUGA; CHF
14	yes	491	76	STI; CHF
16	no	157	80	STI
22	yes	489	0	CHF
25	yes	401	166	STI; MUGA; CHF
29	no	458	55	STI; MUGA; CHF
43	no	182	108	STI; biopsy
55	no	310	12	STI; MUGA; CHF
59	yes	0	177	STI; MUGA; CHF
61	yes	0	91	STI

Abbreviations: STI, systemic time interval; MUGA, multigated acquisition; CHF, congestive heart failure.

gle agent in the doses and schedules used in these studies. Its efficacy is probably comparable to that of most other agents currently used for treatment of breast cancer. Our study suggests a lack of cross-resistance between doxorubicin and mitoxantrone. Seven of 46 patients (15%) responded to one agent after having failed to respond to the other.

The nonhematologic side effects of mitoxantrone are less than those of doxorubicin. Nausea, vomiting, and fatigue are seen less frequently and are less severe. Alopecia to a degree that is bothersome for the patient is unusual, although some hair loss is seen in one third of the patients treated with mitoxantrone. We made no formal evaluation of the quality of life in this study, but the performance status tended to be worse in patients receiving prolonged doxorubicin treatment than in patients receiving prolonged treatment with mitoxantrone. This effect was evident only among patients who responded and not among those whose disease either progressed or showed no change. We have also presented evidence of the cardiotoxicity of mitoxantrone,[13] as have others.[14] Although the crossover design of this study makes it impossible to attribute observed cardiac toxicity to either agent, the incidence of CHF is more than might be expected with doxorubicin alone.

Although doxorubicin may be slightly more effective than mitoxantrone in producing tumor regression of breast cancer, mitoxantrone is clearly less toxic and can produce important responses in patients refractory to CMF. Questions regarding dosing, scheduling, and the optimum use of mitoxantrone have yet to be explored. Much higher doses may be given[15] and may improve antitumor effect. Only a few combinations have been tried, and experience with primary therapy is still limited.

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