Chemotherapy With Mitoxantrone in Combination With Continuous Infusion Vinblastine for Metastatic Breast Cancer

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The efficacy of mitoxantrone in combination with vinblastine was assessed in 156 patients with metastatic breast cancer who had been treated previously with one or multiple chemotherapeutic regimens. Mitoxantrone was given by random assignment, either as a 10 mg/m^2 single intravenous dose or in five consecutive daily fractions of 2 mg/m^2. Vinblastine was given as a continuous intravenous infusion of 1.2 mg/m^2 daily for 5 days. In 115 evaluable patients previously treated with doxorubicin, 21 objective responses (18%) and 11 minor responses (10%) were observed with similar distribution in the two treatment groups. Median time to progression was 27 weeks and 23 weeks, respectively. Eight (32%) of 25 patients who had not received doxorubicin achieved objective remissions and two (8%) had minor responses. Toxic effects were similar for the two treatment schedules. Major toxicities were myelosuppression and neutropenic fever. Other toxicities were mild. Cardiotoxicity, presumably caused by mitoxantrone, occurred in four patients. The combination of mitoxantrone and vinblastine appeared to offer no advantage over single-agent therapy, probably because of the dosage reduction required by the overlapping myelosuppressive toxicity.

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THE MAJORITY OF patients with metastatic breast carcinoma achieve disease remission with front-line chemotherapy, based on combinations of cyclophosphamide, 5-fluorouracil, methotraxate, and doxorubicin.[1-3] Yet complete remissions occur in less than 20% of patients and the duration of remission ranges between 6 and 15 months, with a median survival range of 12 to 24 months. The limited efficacy of the presently available chemotherapy justifies the continuous search for more effective second-line regimens.

We observed that continuous intravenous (IV) infusion improved the therapeutic index of vinblastine in the therapy of breast cancer.[4] Combination chemotherapy with sequential continuous infusion of doxorubicin and vinblastine has produced responses in more than 40% of patients already treated with a nonanthracycline-containing combination.[5]

Mitoxantrone, an anthraquinone compound originally developed to produce a potent quinone-containing antitumor agent free of cardiac toxicity, has significant activity against breast cancer when given either in single IV doses[6] or in five daily fractions.[7] This drug has not shown complete cross-resistance with doxorubicin.[8]

In this study we assess the relative activity and toxicity of two combinations of vinblastine and mitoxantrone, when mitoxantrone was given either as a single dose or in five daily equal fractions.

Patients and Methods

Between January 1982 and October 1984 we treated 156 patients with biopsy-proven metastatic breast cancer. Five additional patients were registered but never received the planned therapy. All patients had received at least one prior chemotherapeutic regimen and signed an informed consent in keeping with the institutional policy. Patients who had received prior therapy with mitoxantrone or vinblastine or had a Zubrod performance status[9] of greater than 3 and a life expectancy of less than 8 weeks were considered ineligible. Patients with active brain metastases or leptomeningeal carcinomatosis were excluded, although exceptions were made for patients with brain metastases that were well controlled by prior radiotherapy. Patients were also excluded in the absence of clearly measurable lesions or adequate bone marrow function, which was defined as normal bone marrow cellularity with a peripheral absolute granulocyte count equal to or greater

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than 2000/μl and a platelet count greater than 100,000/μl. If the inadequate bone marrow reserve was secondary to tumor replacement, patients were considered eligible for treatment in full doses. A final condition for eligibility was a normal cardiac function with normal ejection fraction by multigated cardiac scan or echocardiogram or a cardiotoxicity pathological score lower than or equal to 1.5 by endocardial biopsy or both.[10] Endocardiac biopsy was a mandatory requirement in all patients who had received prior doxorubicin in excess of 350 mg/m^2. All patients were registered with the institutional central data management office prior to receiving therapy. Patients with prior exposure to doxorubicin or other anthracyclines were randomly assigned to one of two different schedules. Group 1 received mitoxantrone at 2 mg/m^2 IV over 20 to 30 minutes daily in the first 5 days of each cycle, each dose was diluted in 200 ml of 5% dextrose in water (Treatment 1). Group 2 received mitoxantrone at 10 mg/m^2 in 250 ml of a 5% dextrose solution on the first day of each cycle (Treatment 2). Vinblastine was given as a 5-day continuous infusion of 1.2 mg/m^2 daily in both treatment schedules. Poor-risk patients, defined as those with inadequate bone marrow reserve or abnormal liver function (bilirubin greater than 2 g/dl, transaminases greater than twice the upper normal values), received the drugs at a 20% reduction.

To avoid the likelihood of severe tissue necrosis from extravasation, the drugs were infused via long-term percutaneous silicone elastomer central venous catheters.

To assure a balanced distribution into the two treatment arms, the patients were stratified before randomization based on performance status, dominant site of disease, and number of organ sites involved.

A third arm of this study (Group 3) was designed to evaluate patients with no prior exposure to anthracyclines. Those patients received their therapy in accordance with treatment schedule 2.

The courses of therapy were repeated at 3-week intervals provided sufficient hematologic recovery had occurred. Leukocyte and platelet counts were obtained at weekly intervals, and renal and liver functions were assessed before each course. A cardiac scan or echocardiogram was performed before every other course of therapy. Endomyocardial biopsies were generally repeated after every fourth course of therapy in patients who had received prior doxorubicin at doses greater than 350 mg/m^2. The protocol called for discontinuation of therapy at any time that an endomyocardial biopsy showed a grade 1.5 pathologic change or severe cardiac dysfunction occurred.

The response to therapy was assessed in all patients by at least two staff oncologists. Tumor measurements by radiographs, scans or sonograms were reviewed with specifically competent radiologists whenever the interpretation was difficult or debated. A complete response was defined as the disappearance of all clinical or laboratory evidence of malignant disease in an asymptomatic patient for at least 4 weeks. A partial remission was defined as a 50% or greater decrease in the sum of the products of the diameters of measured lesions of at least a 4-week duration. If malignant hepatomegaly was used as an indicator, a partial remission was defined as either a 3-cm reduction in hepatomegaly or a 50% reduction in the sum of the liver enlargements below the costal margin in both midclavicular lines plus the epigastric line. However, responses in hepatic metastases were always confirmed by imaging tests. Minor response was defined as an objective response of less than 50% in the sum of the products of the diameters of the measurable lesions. A steady state of disease with neither objective improvement nor progression over eight weeks was defined as no change. Progressive disease was defined as the unequivocal increase in the size of any of the measured lesions or the appearance of any new lesion. For unchanged and responding patients, time to progression was calculated from the onset of therapy to the date of earliest documentation of disease progression. Statistical differences in response rates seen in the patient subsets were analyzed by the chi-square test.

Results

Six patients were retrospectively considered not eligible. Three had presented either with a performance status of 4 or with a predictable survival of fewer than 8 weeks. Two others had received prior continuous infusion of vinblastine, and the last one had no measurable disease. Ten patients were considered not evaluable. Three had received concomitant, additional chemotherapy or hormonal therapy. One, who erroneously received a twofold dose of mitoxantrone with significant toxicity, refused further treatment. Two were lost to follow-up, and one died of progressive disease and a preexisting infection during the administration of the first treatment. Two patients who died 2 weeks after onset of therapy, one of progressive disease, the other of neutropenic sepsis, and a third patient who refused to continue because of poor tolerance, could not be evaluated for response. The three patients were considered to be toxic failures.

As shown in Tables 1 and 2, the pretreatment characteristics of patients in Groups 1 and 2 were comparable. Patients in group 3 are examined separately.

The responses seen in 140 evaluable patients are shown in Table 3. The two groups previously exposed to anthracyclines had similar results with an overall response rate of 18%. The higher response rate in Group 3 was not statistically different, because of the small num-

TABLE 1. Pretreatment Characteristics of Responding Patients

Accession no.	Treatment group	Response	Age (years)	Zubrod performance	Site of metastases
3	2	PR	53	0	Skin
4	2	PR	30	1	Breast, skin
6	2	PR	41	1	Breast, nodes, bones, marrow
10	1	PR	62	0	Skin, nodes
12	3	PR	62	0	Nodes
16	2	PR	67	1	Lung
20	2	PR	45	3	Skin, bones
26	1	PR	66	0	Breast, skin, nodes
32	1	PR	62	0	Nodes
38	2	PR	49	1	Bones, lung
43	1	PR	38	2	Bones (brain)
44	2	PR	56	3	Bones, pleura, liver, (brain)
59	2	PR	59	1	Breast, skin, nodes, bones, liver
73	1	PR	67	0	Skin, marrow
76	2	CR	33	0	Skin
81	3	CR	51	1	Nodes
83	1	CR	42	0	Lung
87	1	PR	48	1	Bone, marrow, lung, liver
89	3	PR	47	0	Bone, marrow
104	2	PR	38	1	Breast, nodes
105	1	PR	62	1	Skin, nodes, pleura
106	3	PR	48	0	Liver, intraabdominal nodes
115	3	PR	60	1	Bones
118	2	PR	59	0	Skin, nodes, bones
122	3	PR	50	2	Breast, skin, bone, pleura
128	3	PR	34	1	Bones
150	2	PR	63	0	Bones, lung, liver
153	1	PR	63	1	Bones, marrow
161	2	PR	46	0	Bones, marrow

PR: partial response; CR: complete response.

ber of patients. Median time to progression was 27 weeks for responders, 23 weeks for those with minor response, and 14 weeks for those with unchanged conditions. The durations were comparable for all groups.

Responses occurred in 35% of patients with the soft tissue as dominant site of disease, compared to 21% for those with dominant bone and 14% for those with dominant visceral metastases ($P = 0.05$). Twenty-five percent of patients with only one or two sites of metastasis and 14% of those with three or more sites responded ($P = 0.16$). Responses were seen in 30% of patients who had undergone only one prior therapy, 15% of those with two, and 4% of those with three or more ($P = 0.01$). Remissions occurred in 43% of patients with performance score of 0, 17% with performance of 1, and 10% with performance of 2 or 3 ($P < .01$). There was no correlation of response with age, premenopausal status, and duration of prior chemotherapy.

Toxicity

Toxicity was assessed in 156 patients, who received 697 courses of therapy. Types and distribution of toxic effects were similar for the two drug regimens. The me-

TABLE 2. Patients Characteristics

	Group		
	1	2	3
No. of patients	53	62	25
Median age in years (range)	53 (27–67)	53 (29–68)	48 (28–71)
Percent premenopausal	38	42	40
Median Zubrod performance status (range)	1 (0–3)	1 (0–3)	1 (0–3)
Dominant soft tissue disease (percent)	21	23	24
Bone disease (percent)	24	27	32
Visceral disease (percent)	55	50	44
Median number of metastatic sites (range)	2 (1–6)	2 (1–6)	2 (1–5)
Median number of prior chemotherapeutic regimens (range)	2 (1–4)	2 (1–6)	1 (1–2)
Median duration of prior chemotherapy in months (range)	16 (3–38)	14 (2–35)	12 (3–31)

dian lowest absolute granulocyte count was 520/μl, generally on day 14, with a range of 0 to 2800/μl. The median lowest platelet count was 193,000/mm^3 (range, 12,000 to 437,000/μl), most commonly on day 8.

The other toxicities seen are shown in Table 4. Gastroenteric, neurologic, and general toxic effects were mild to moderate. Subclavian vein thrombosis occurred in one patient as a complication of her indwelling central venous catheter.

Fever with neutropenia was a common occurrence, and sepsis was documented in nine patients. One, who was not evaluable for response because of a major protocol violation and very poor performance, died of septic complications after the second course. A second patient died of sepsis on day 13 of the first cycle and was counted as a toxic failure.

Particular attention was given to the possibility of cardiac toxicity, since most of the patients had received prior doxorubicin at a median dose of above 400 mg/m^2. Cardiac toxicity was documented in four patients, two for each treatment schedule. One patient, who had received 450 mg/m^2 of doxorubicin, developed clinically symptomatic congestive heart failure after 50 mg/m^2 of mitoxantrone. Her ejection fraction by cineangiocardiography declined about 25% from the pretreatment value. In two patients who had previous doxorubicin doses of 400 mg/m^2, the ejection fraction dropped more than 20% following administration of 44 and 75 mg/m^2 of mitoxantrone. Although they had no evidence of overt cardiac decompensation, mitoxantrone was discontinued. One additional patient was taken off treatment after receiving 200 mg/m^2 of mitoxantrone and 240 mg/m^2 of prior doxorubicin because of a greater than 15% drop in the ejection fraction, and an abnormal response to exercise.

The chemotherapy tolerance was similar in all treatment groups. Myleosuppression was the dose-limiting toxicity. Respective starting and final dose averaged 98% and 90% of that recommended.

TABLE 3. Results

	Total	Group 1	Group 2	Group 3
Patients				
Entered	161	61	71	29
Not treated	5	4	—	—
Not eligible	6	2	4	—
Not evaluable	10	2	5	3
Evaluable	140	53	62	25
Responses				
Complete	3	1	1	1
Partial	26 (21%)	8 (17%)	11 (19%)	7 (32%)
Minor	13	6	5	2
No change	46	16	24	6
Progressive disease	52	22	21	9

Discussion

The activity of mitoxantrone in the treatment of breast cancer has been studied by different investigators at different schedules of administration.[6–8] The patient populations in these studies are probably not comparable. Therefore, in the absence of a randomized trial, it is impossible to assess whether one treatment schedule may be superior. In our study, the two treatment schedules of mitoxantrone, in combination with vinblastine, appeared to have similar activity and toxicity.

These agents have produced similar or higher response rates when used singly in similar patient groups.[4,6,7] Additionally, in patients with no prior exposure to anthracyclines, our combination appeared to be less effective than a combination of vinblastine and doxorubicin.[5] At the doses and schedules studied, vinblastine and mitoxantrone appeared to have no synergistic activity in breast cancer patients. Their overlapping myelotoxicity prevented the possibility of combining them in full doses. Further dose reduction became necessary in many of our patients because of the myelosuppression that the higher doses induced. Consequently, the low response rate observed in our study was explained by the low dosages employed for both agents and their steep dose–response curves.[4,11]

With the exclusion of myelosuppression and the related high incidence of neutropenic fever, the other toxicities were generally mild, and chemotherapy was well tolerated by the patients.

We documented cardiotoxicity in four patients, confirming other reports that have established this as a mi-

TABLE 4. Toxicity in 156 Patients

Type of toxicity	Percentage of patients affected
Nausea/emesis	19
Mucositis	10
Weight loss	5
Diarrhea	1
Weakness/fatigue	6
Constipation	6
Peripheral neuropathy	4
Tremor	2
Myalgias	1
Anemia	4
Alopecia	1
Chemical hepatitis	2
Venous occlusion	1
Fever with leukopenia	23
Fever without leukopenia	3
Sepsis	7
Septic death	1
Myocardial dysfunction	4

toxantrone-related toxicity.[12,13] In our patients, cardiotoxicity occurred both with single or fractionated doses of mitoxantrone. This suggests that with mitoxantrone, unlike doxorubicin, a short peak drug exposure may not be more detrimental to the heart than a steadier lower concentration. The small number allows no statistical validity to our observation.

The combination of mitoxantrone and continuous infusion vinblastine was not advantageous. The agents have interesting activity when given alone, and further investigations of their activity in combination with other agents, possibly without significantly overlapping toxicity, may be worthwhile.

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