Mitoxantrone, Cyclophosphamide, and Fluorouracil in Metastatic Breast Cancer Unresponsive to Hormonal Therapy

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Fifty-two patients with hormonally unresponsive or estrogen receptor negative metastatic breast cancer who had not received prior chemotherapy received mitoxantrone 10 mg/m^2, cyclophosphamide 500 mg/m^2, and 5-fluorouracil 1000 mg/m^2 (MCF) by short intravenous infusion every 21 days. Disease that was resistant or stable to this regimen was treated with doxorubicin 25 mg/m^2/day for two days and vinblastine 1.4 mg/m^2/day for four days (DV). Both drugs were given by continuous infusion. Thirty-one partial remissions and four complete remissions occurred after treatment with MCF. Only thirty-four evaluable patients crossed to the DV phase with partial remission (11 patients), stable (five patients), or resistant (18 patients) disease. Eleven patients' responses were upgraded. The median overall time to progression (TTP), defined as the sum of the TTP on MCF and TTP on DV, was 12 months. The median survival of all patients was 19 months. Granulocytopenia was the dose limiting toxicity for MCF, but cumulative thrombocytopenia was noted. Nausea and vomiting occurred in most patients but was mild. Severe alopecia occurred in half the patients. One patient developed congestive heart failure after receiving a cumulative dose of 206 mg/m^2 of mitoxantrone. The incidence of infectious complications was 35% on each regimen; 50% of these were mild. MCF is an effective combination that was well tolerated. Objective responses, durations of response, and survival were similar, but not superior, to standard doxorubicin-based combinations. Toxicity was somewhat less.

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THE SURVIVAL of patients with untreated breast cancer is variable.[1] Some studies suggest that treatment with combination chemotherapy has improved survival time from first metastasis, especially in patients who respond to therapy.[2–4] In some studies, the use of a doxorubicin based combination is associated with an increase in objective response rates and duration of responses compared with non-doxorubicin combinations.[3,5–7] In other studies, the duration of response in responding patients was not different.[8] However, in these comparative studies, the impact on longterm survival has not been significantly different.[7] Response to hormone therapy or a positive estrogen receptor (ER+) was associated with longer survival in some retrospective reviews,[3,9–15] but not in others.[16–18] Treatment was quite variable in these studies. Prospective studies of patients given adjuvant chemotherapy do show both longer survival and disease-free survival in ER+ patients.[19] Whether ER status or response to hormone therapy affects response to chemotherapy is controversial.[20,21] In some studies, patients with hormonally unresponsive tumors had a shorter duration of objective remission compared with patients with hormonally responsive tumors.[15,22–24] Thymidine labeling index is higher in ER negative tumors.[25,26] Rapid growth rates and genetic instability associated with a high labeling index would explain the shorter remission durations and the poorer prognosis seen in patients with ER negative or hormonally unresponsive tumors.[20,27] These data have led some investigators to design innovative and aggressive therapeutic strategies for patients with ER negative or hormonally unresponsive tumors.[28]

Mitoxantrone is an anthraquinone that intercalates with DNA. It lacks the amino sugar moiety of doxorubicin and this suggested that it might be less tropic to and, thus, less toxic to cardiac muscle. In our Phase II trial, 27 patients with advanced metastatic breast cancer refractory to conventional treatment were treated with mitoxan-

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TABLE 1. Patient Characteristics and Treatment Results in Hormonally Unresponsive Metastatic Breast Cancer

	Current study MCF-DV	Historical FAC
No. entered	56	—
No. evaluable	52	69
Median age (years)	51	53
Range	27–76	24–73
Median Zubrod performance status	1	1
Range	0–3	0–3
Median disease-free interval (mos)	11	12
Range	0–234	0–280
Menopausal status		
% Premenopausal	47	35
Median no. disease sites	2	2
Range	1–6	1–6
% Patients with visceral dominant disease	63	54
Response rates		
CR (%)	8	26
PR	61	52
SD	25	12
PD	7	10
Median time to progress (mos)	12	14
Range	(3–45+)	(2–64+)
Median survival for all patients (mos)	19	19
Range	(4–45+)	(2–64+)

MCF: mitoxantrone, cyclophosphamide, and 5-fluorouracil; DV: doxorubicin and vinblastine; FAC: 5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide; CR: complete remission; PR: partial remission; SD: stable disease; PD: progression of disease.

trone. Six patients (22%) had objective responses. Two of these patients had progression of disease while receiving a doxorubicin combination, thus suggesting incomplete crossresistance to mitoxantrone. The median duration of response exceeded 6 months. Myelosuppression was the dose limiting toxicity.[29] In previously untreated patients in another Phase II study of mitoxantrone, objective responses were seen in 33%.[30] Additional evidence of both similar efficacy and incomplete crossresistance to doxorubicin came from preliminary results of a randomized trial comparing mitoxantrone with doxorubicin in patients with advanced breast cancer who had received minimal prior chemotherapy.[31] There was no significant difference in response rates or durations. Upon failure to respond to the initial drug, the alternate treatment was given. Secondary responses were seen with equal frequency in both arms. Later results have confirmed these early observations.[32]

These early studies showed a lower incidence and lesser degree of acute drug toxicity, nausea, vomiting, and alopecia, compared with doxorubicin. Similarly, cumulative cardiotoxicity due to mitoxantrone occurred less often. This suggested that patients at high risk of relapse could be maintained in a remission status for a longer period of time because therapy would not need to be withdrawn prematurely to prevent cumulative cardiotoxicity. Additionally, the morbidity of treatment with mitoxantrone would be less so that patients could tolerate continued treatment.

For these reasons, mitoxantrone was substituted for doxorubicin in a combination of proven efficacy, 5-fluorouracil, Adriamycin (doxorubicin) and cyclophosphamide (FAC),[33–36] to develop an effective but less toxic induction regimen, mitoxantrone, cyclophosphamide, and fluorouracil (MCF), for patients with metastatic breast cancer unresponsive to hormonal therapy and without prior chemotherapy treatment. Since this subset of patients is at high risk of early relapse, doxorubicin in combination with vinblastine sulfate (DV) was designed as a potentially noncrossresistant regimen for a maintenance or reinduction phase after MCF. In our experience, DV produced a 43% response rate in patients with metastatic breast cancer who had failed prior treatment with cyclophosphamide, methotrexate, and fluorouracil.[37] The median time to progression (TTP) was 10 months for responding patients. These results indicated that the combination of DV had significant antitumor activity despite prior chemotherapy. We hypothesized that sequential use of two potent and potentially noncrossresistant regimens should lead to a superior response rate, duration of response and, most important, survival in this subset of patients.

Material and Methods

Patients without prior chemotherapy for metastatic breast cancer who had a Zubrod performance status of three or less and who were ER negative or unknown or had failed to respond to hormonal therapy were eligible.[38] Since frequent evaluations were necessary only patients who were able to return regularly were considered. Fifty-six patients who met these criteria were seen at University of Texas M. D. Anderson Hospital between June 1982 and July 1983. The patients' characteristics are described in Table 1. Patients had a good performance status and a short disease-free interval. Menopausal status was almost equally divided between premenopausal and postmenopausal. All but eight patients were ER negative. Two patients who were ER positive had failed a previous trial with hormones. Six ER unknown patients had visceral disease, a short disease-free interval, or had failed hormones. Most patients had visceral disease as the predominant site of disease.

Induction chemotherapy consisted of mitoxantrone 10 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 1000 mg/m^2 by a short intravenous injection on day 1 of each 21 day cycle. If disease progressed after two cycles, remained stable after six cycles, or stabilized after three cycles of MCF following an initial objective response, the second phase of treatment was instituted with doxorubicin 50 mg/m^2 by continuous infusion over 48 hours and vin-

blastine 1.4 mg/m^2 over 24 hours daily for 4 days. Cycles were repeated every 21 days or later pending recovery of the granulocyte count to $\geq 1500/\mu l$ and the platelet count to $\geq 100{,}000/\mu l$.

Doses of subsequent cycles were determined by the extent of myelotoxicity. Serious infection or hemorrhage related to myelosuppression required a 20% dose reduction for subsequent cycles. If the lowest recorded granulocyte count was $<500/\mu l$, or the lowest recorded platelet count was $<50{,}000/\mu l$, doses of drugs were decreased by 20%. If the lowest recorded granulocyte count was $>1500/\mu l$ and the lowest recorded platelet count was $>100{,}000/\mu l$, all doses of drugs were increased by 20%. Chemotherapy was given for a total of 2 years, or for 1 year after achieving complete remission (CR), whichever was the shorter. Patients who achieved partial remission (PR) continued to receive chemotherapy until treatment failure, or for a total of 2 years, whichever came first. When it was feasible, local consolidation was given with radiotherapy or surgery to areas of residual disease or to initial sites of bulky disease at the time systemic chemotherapy was discontinued in responding patients.

A written informed consent approved by the Institutional Review Board was obtained from each patient. A complete history was obtained, and the following tests were performed: physical examination with documentation of performance status and tumor measurements; a complete blood count with differential and platelet counts; serum protein, albumin, calcium, phosphorus, glucose, uric acid, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and aspartate aminotransferase (SMA-12); carcinoembryonic antigen (CEA) assay; urinalysis; electrocardiogram (ECG); liver ultrasound or computed tomography; bone scan; bone survey; chest radiograph; isotope cardiac scan with ejection fraction (EF), or echocardiogram with EF; and mammogram. Other radiologic or isotope studies or bone marrow aspiration and biopsy were performed when clinically indicated. A complete blood count with differential and platelet counts was determined weekly. An SMA-12 and CEA assay were performed before each cycle of therapy. Initially, an ECG was repeated after every one or two cycles of treatment, after a total cumulative dose of 20 to 30 mg/m^2 of mitoxantrone, or after a total cumulative dose of 200 mg/m^2 of doxorubicin was reached. Subsequently, as more clinical experience was acquired, ECGs were performed after every four cycles. A chest radiograph was obtained every 2 to 3 months or more often as clinically indicated. Bone and liver scans, ultrasound, or CT were done every four cycles, and mammograms were performed yearly or as clinically indicated. Bone marrow aspiration and biopsy examinations were performed in patients who had myelosuppression for more than 6 weeks after any cycle of chemotherapy to exclude tumor invasion as the cause of pancytopenia.

A cardiac scan with EF was performed after each 20 to 30 mg/m^2 cumulative dose of mitoxantrone. As more clinical experience was gained, cardiac scans were deferred until completion of each 40 to 60 mg/m^2 cumulative dose of mitoxantrone. Before crossover to DV, a cardiac scan, ECG, and an endomyocardial biopsy were performed. Endomyocardial biopsies were graded on a modified Billingham scale.[39] The cardiac scan was repeated after each 200 to 250 mg/m^2 cumulative dose of doxorubicin. If the EF decreased by 15%, if 350 to 400 mg/m^2 of doxorubicin had been administered, or if the cardiac scan EF was between 50% and 64%, an exercise isotope cardiac scan and endomyocardial biopsy were obtained. Thereafter, an isotope cardiac scan and ECG were repeated after every two cycles of DV, and an endomyocardial biopsy was performed after every fourth course, or earlier if indicated.

Determination of response was based on standard International Union Against Cancer (UICC) definitions.[40] Time to response (TTR) was measured from the initiation of MCF therapy until the first evidence of response. TTP was the interval from start of MCF therapy until evidence of relapse. If treatment was changed to DV and the patient had an objective response or showed no change, the overall TTP for a given patient was defined as the sum of the TTP during MCF therapy plus TTP during DV therapy. Survival was measured from the start of MCF therapy until death from whatever cause.

To define our experience with FAC chemotherapy in patients whose tumors were ER negative or borderline, records of patients who had ER measured on the primary tumor and who were treated with one of two sequential FAC protocols from 1979 to 1981 were reviewed. These studies showed no significant difference in response rates or durations when compared with each other or with the standard FAC treatment and will thus be designated "FAC".[41,42] The characteristics of this population are described and compared with the current study population in Table 1. Of 283 evaluable patients treated with FAC from 1979 to 1981, 59 had documented ER negative tumors and another ten patients had borderline values. Characteristics of patients receiving MCF were compared with those of patients receiving FAC by using the chi-square test or the Mann-Whitney test as appropriate. The Kaplan-Meier method was used to calculate curves that described the distribution of survival times for groups of patients.[43] Differences among distributions were tested using a generalized Wilcoxon test for two curves.[44]

Results

Four patients could not be evaluated for response. Two patients did not have measurable disease; two patients refused further therapy after one and two courses each.

The median TTR for patients on MCF was 2 months

TABLE 2. Response to MCF and Crossover DV

Best MCF response		Response status at crossover	Response to DV n = 34		
n = 52		n = 34	CR	PR	No response
CR	4	—	—	—	—
PR	31	11	3*	8	—
SD	13	5	—	2	3
PD	4	18	1	5	12

MCF: mitoxantrone, cyclophosphamide, and 5-fluorouracil; DV: doxorubicin and vinblastine; CR: complete remission; PR: partial remission; SD: stable disease; PD: progression of disease.

* One responding patient rendered CR with surgery.

(range, 1–5 months). Table 2 shows the response to MCF and DV. The first column shows the response to MCF. Thirty-five objective responses were seen for a response rate of 68%. Only four patients had progressive disease during initial MCF therapy. One patient who achieved CR with mitoxantrone relapsed at 8 months. A second patient, who achieved CR in lung metastases after three courses, discontinued MCF because of the expense of travel at 4 months. She received other chemotherapy and relapsed in the brain 30 months later. The remaining two patients have been in unmaintained remission for 34+ and 45+ months. The median TTP for 31 patients who attained a PR on MCF was 7 months.[2–17]

The second column of Table 2 shows the status of patients at crossover. Only thirty-eight patients crossed to the DV arm. Fourteen patients were not eligible for crossover for the following reasons: four patients had CR; five patients died; and five patients crossed to other therapy, for example, hepatic arterial therapy or other drugs. Of the remaining 38 patients who did cross to DV, four patients were not evaluable for response. One patient died on day 2 of her first course of therapy and pulmonary embolism was suspected. Two patients failed to return for evaluation after crossover. One patient who had excellent pain reduction and regression of supraclavicular and axillary masses, had recurrence of pain in the axilla without a change in the CT scan. She received radiation therapy to the axilla and subsequent DV chemotherapy but had no measurable disease.

The remaining columns show the response to DV. Patients who attained a CR on MCF did not receive DV. Of 31 patients achieving PR on MCF, only 12 remained in PR at the time of crossover and one of these patients did not receive further chemotherapy. Only 11 patients in PR crossed to alternate therapy. Nine patients received DV. Two patients received vinblastine alone because of concerns of cardiac toxicity. One of these patients had a near normal EF and upon progression subsequently did receive doxorubicin without problems. The 18 patients with progressive disease at the time of crossover included 11 patients who had relapsed from PR, one patient in CR who relapsed, three patients who initially had shown no change while receiving MCF, and three patients who had progression of disease after initial treatment with MCF.

Four patients achieved CR after crossover to DV; three patients had previously attained PR on MCF and were in PR at the time of crossover. The remaining patient had progressive disease at the time of crossover, after an initial PR on MCF. Of the three CRs in patients who crossed in PR status, one patient who initially had an advanced primary breast tumor, was rendered surgically free of disease (FOD). She had demonstrated further response after one course of DV and underwent debulking mastectomy. She received consolidation treatment with radiation, discontinued chemotherapy, and was FOD at 26+ months. A second patient, who also had consolidation with radiation to the previous area of bulky disease after she attained CR, remains FOD at 34+ months. The remaining two patients relapsed at 4 and 16 months respectively after attaining CR.

Fifteen patients were in PR after crossover to DV (Table 2). Eleven patients had crossed in PR; three became CR thus, leaving eight patients who remained in PR on DV. In the remaining seven patients treatment with DV upgraded the response to MCF. Two patients with previously stable disease and five patients with progressive disease on MCF after an initial PR attained PR with DV. Of these seven patients who attained a PR with DV, the median TTP after crossover was 7 months (range, 3–20 months).

Figure 1 shows that the median overall TTP for responding patients is 12 months (3–45+ months). The median survival for all patients is 19 months (4–45+ months).

The characteristics of the historic cohort of patients whose tumors were ER negative and who received FAC chemotherapy were not significantly different from the study population (Table 1). While CR was more frequent with FAC than with MCF, ($P = 0.03$, chi-square), there was no significant difference in the objective response (CR + PR) between the two populations ($P = 0.18$, chi-square) nor in the median overall TTP or median survival in patients who responded to either treatment.

Toxicity

Hematologic effects are shown in Table 3. Granulocytopenia was the dose limiting toxicity with MCF and required a reduction in subsequent dosage. The median lowest recorded platelet count in courses three and six was significantly lower than in course one ($P = 0.03$ and $P = 0.01$, respectively; Mann-Whitney test), suggesting cumulative thrombocytopenia. Granulocytopenia was dose limiting with DV, but there was no evidence of any cumulative myelotoxicity.

The incidences of other toxicities are shown in Table 4. MCF produced less emesis than our previous experience with doxorubicin, administered as an intravenous bolus in combination with 5-fluorouracil and cyclophosphamide, which caused nausea and vomiting in 90% of patients. Nausea and vomiting was mild in one-third of patients who experienced it on MCF. The low incidence of nausea and vomiting with DV is similar to our reported experience with continuous infusion DV.[37] Moderate to severe mucositis was more common with DV, as expected.

Total alopecia occurred in 50% of the patients on MCF. Thinning of the hair that did not require use of a wig occurred in 20% of patients. This is in marked contrast to nearly 100% in our prior experience with FAC.

Infectious complications occurred with equal frequency in both phases of the trial. Approximately 50% of the fevers of unknown origin (FUO) during neutropenia were mild. If fever was less than 38.3°C or the patient did not appear ill after full evaluation and cultures were taken, oral antibiotics were given. These patients did not require hospitalization.

Evaluation of the cardiac toxicity of mitoxantrone in this study is limited since the median cumulative dose was only 66 mg/m^2. The highest cumulative dose of mitoxantrone was 206 mg/m^2. The same patient also received 80 mg/m^2 of doxorubicin and developed pulmonary edema. The EF was 44%, but the patient became assymptomatic after treatment with digoxin and furosemide. One patient, who had received 110 mg/m^2 of mitoxantrone, had a progressive decrease in EF and experienced exertional dyspnea 1 year after discontinuation of mitoxantrone. The EF measured 43%. Symptoms improved with digoxin. A third patient received 20 mg/m^2 of mitoxantrone and 300 mg/m^2 of doxorubicin and was assymptomatic, but the EF decreased from 72% to 53%. A cardiac biopsy specimen showed Grade 1.0 changes.

There were a total of 35 patients who underwent 45 endomyocardial biopsies. Our data do not show any significant difference between the dose of mitoxantrone causing Grade 0.5 *versus* Grade 1.0 endomyocardial biopsy specimen scores. In one patient, a biopsy specimen score of Grade 1.0 decreased to Grade 0.5 with further mitoxantrone. No patient had evidence of serious myocardial injury, manifested as an endomyocardial biopsy specimen score of more than Grade 1.5, during either phase of the study.

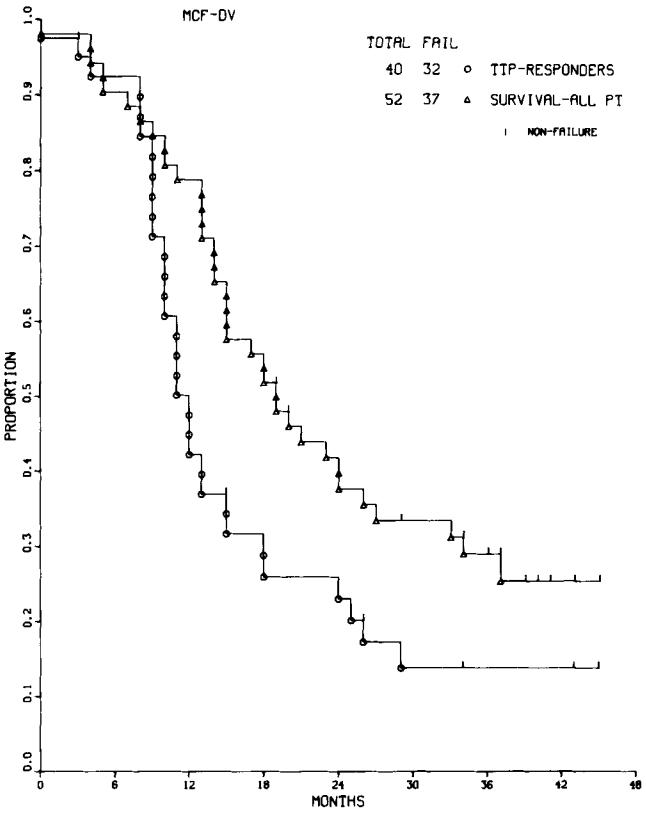

FIG. 1. Actuarial survival and time to progression for patients treated with mitoxantrone, cyclophosphamide, and 5-fluorouracil (MCF).

TABLE 3. Hematologic Effects: MCF

	Cycle number				
	1	3	6	10	13
Granulocyte count					
Median lowest	380	478	490	608	420
Range	0–5550	20–1700	0–1539	225–1445	312–744
No. of courses	41	32	23	11	5
Platelet count			†		
	*				
Median lowest	192	151	97	151	85
Range	22–431	38–393	36–292	45–234	14–204
% Protocol dose					
Median	100	100	90	80	80
Range	80–110	66–145	70–145	70–120	50–120

MCF: mitoxantrone, cyclophosphamide, and 5-fluorouracil.
* Mann-Whitney, $P = 0.03$.
† Mann-Whitney, $P = <0.01$.

TABLE 4. Other Toxicity: MCF-DV

Toxicity	Patients MCF	DV
Nausea/vomiting (%)	88	17
Stomatitis moderate-severe (%)	17	26
Alopecia severe (%)	54	67
FUO during neutropenia (%)	35	31
Documented infections (%)	37	35
Sepsis/pneumonia (%)	12	12
No. of patients with congestive heart failure	0	1
No. of patients with 15% decrease in cardiac ejection fraction	1	2

MCF: mitoxantrone, cyclophosphamide, and 5-fluorouracil; DV: doxorubicin and vinblastine; FUO: fever of unknown origin.

Discussion

The overall response rate to MCF was similar to our previous experience with doxorubicin combinations.[33–36] The 8% CR rate with the MCF phase was lower than the 15% to 20% we have consistently seen with combinations containing doxorubicin; however, the sample size is small and the confidence limits range from 2% to 19%. This may also be a reflection of tumor biology and variation in patient characteristics. The median disease-free interval in this study was 11 months compared with 15 months in our previous FAC studies, and more patients who received MCF were premenopausal, despite the similar median age of both populations. Sixty-four percent of these patients had visceral disease, and this is similar to our historic FAC population. The incidence of osseous *versus* soft tissue disease was reversed, however, and more patients in our study had soft tissue disease.

A subset of patients who received FAC in the years immediately preceding the current study and who had a negative or borderline value of ER measured on the primary tumor, were reviewed. There were no significant differences in characteristics, overall objective response rate, TTP, or survival between both groups. While this comparison is retrospective, it does not suggest any advantage of mitoxantrone given in this dose and schedule for this subset of patients. In fact, when results were analyzed by separate phases of the study it was clear that DV contributed significantly to prolonging the overall TTP since seven of the 15 PR patients on DV were upgraded from stable or progressive disease on MCF. This was not the case with the maintenance arm (cyclophosphamide, methotrexate, and 5-fluorouracil) of the historic FAC study. This suggests that, despite incomplete crossresistance with doxorubicin, MCF may be a less potent induction regimen than FAC.

Our previous studies have also shown that response occurs independently of the site of disease but is significantly related to the overall tumor burden.[24] Tumor burden was comparable in this group of patients and in our prior FAC study population. The combined CR rate for both phases of the current study, however, was 16% (confidence intervals 7% to 29%) and this was more consistent with our experience with FAC given with maintenance cyclophosphamide, methotrexate, and 5-fluorouracil.[33–36]

In our Phase II study of mitoxantrone, responses were not seen in metastatic liver lesions.[29] Of nine patients with liver involvement in this study, six had extensive hepatic disease. Responses were seen in seven patients. Similarly, other investigators observed limited responses to metastases in the lung; they suggested mitoxantrone had decreased efficacy in pulmonary lesions.[30] Twenty patients in this study had pulmonary disease. In 18 patients, the extent of disease was moderate to severe. Responses were seen in 12 patients with lung involvement.

This study also suggests that local control at sites of bulky disease is enhanced by combined modality approaches. Of the eight patients in CR, four had local consolidation treatment with surgery or radiotherapy or both at the completion of chemotherapy. One additional patient with disease progression on DV was FOD after surgery and radiotherapy. All five patients were FOD without therapy from more than 5 to 19 months. Our previous studies have shown that the initial sites of disease are the most common sites of relapse in patients who attain a CR with combination chemotherapy that includes doxorubicin.[15] These relapses usually occurred within 1 year after discontinuation of therapy. Similarly, we have used combined modality approaches in patients who have isolated recurrences to remove all gross disease before initiation of adjuvant chemotherapy.[45] The results suggested that more aggressive local therapy resulted in improved local control.

Prolonged thrombocytopenia requiring discontinuation of mitoxantrone was reported by Stuart-Harris in three patients with extensive liver metastases who had received more than 6 months of treatment with mitoxantrone.[46] In that study, patients received 12 to 14 mg/m^2 of mitoxantrone by short intravenous infusion every 3 weeks. Only one patient had prior chemotherapy. Bone marrow aspiration was reportedly normal in two of these patients. As in most other reports, cycle by cycle myelotoxicity data was not provided to assess the possibility of cumulative toxicity. We observed cumulative thrombocytopenia.

In our study, only six patients had extensive liver involvement. In all cases but one, the lowest recorded platelet count was near or above the median for that course, suggesting that extensive liver involvement alone could not account for cumulative thrombocytopenia in this population. However, pharmacokinetic studies in patients with hepatic impairment or third space have shown that the average total clearance of mitoxantrone was less than

one-half of that in patients with normal liver function, and the average terminal half-life was almost doubled.[47] In that study, only one patient received a dose of mitoxantrone that approached the doses used currently. However, no dose dependent mitoxantrone-pharmacokinetics were observed.

Mitoxantrone is clearly cardiotoxic in patients without prior exposure to anthracyclines. One patient in our study developed pulmonary edema after she had received 206 mg/m^2 of mitoxantrone. Other studies have shown congestive heart failure occurred in patients, who had not received prior doxorubicin, at doses of 160 to 170 mg/m^2 of mitoxantrone.[48] Only nine patients in this study received a cumulative dose of mitoxantrone $\geq$ 100 mg/m^2. As defined by equitoxic doses to bone marrow, this is approximately equivalent to 500 to 550 mg/m^2 of doxorubicin. Whether this is a valid basis for comparison of cardiotoxicity is disputed by some.[49] Due to the small numbers of patients in this study receiving mitoxantrone at doses above 100 mg/m^2, no valid comments on the incidence of mitoxantrone-induced cardiotoxicity are warranted. Whether the therapeutic index of mitoxantrone can be augmented by continuous infusion remains to be demonstrated. This may become an important question since recent information suggests mitoxantrone has a steep dose-response curve.[50] Optimum use of mitoxantrone may require administration of twice the current standard dose. We are currently evaluating mitoxantrone as a single agent at a starting dose of 25 mg/m^2 in patients with breast cancer who have not received prior doxorubicin.

In summary, MCF is an effective, well tolerated combination for patients with metastatic breast cancer. Comparison of objective responses, durations of response, and survival with a statistically similar group of patients who were treated with FAC in the years before this study did not show any advantage to this combination. Since the fraction of patients on MCF who were salvaged on crossover to the DV arm contributed to those results, there is a suggestion that MCF may not be as potent an induction regimen as the standard FAC. However, this is a small study.

In view of the advantages of decreased acute toxicity, innovative strategies for optimizing the efficacy of mitoxantrone should be pursued. These may include higher doses of mitoxantrone with or without bone marrow rescue.

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