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ORIGINAL ARTICLE

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Phase II study of mitoxantrone by 14-day continuous infusion with granulocyte colony-stimulating factor (GCSF) support in patients with metastatic breast cancer and limited prior therapy

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Abstract *Purpose*: Early phase II evaluation of intravenous bolus mitoxantrone indicated objective response rates of 17–36% in patients with metastatic breast cancer. Subsequently, it has been suggested that continuous infusion may be the optimal way to administer this drug in order to achieve maximal cytotoxic effect with minimal toxicity. We present the results of a phase II study that evaluated the efficacy and side effects of mitoxantrone administered at the maximally tolerated dose by continuous infusion in patients with metastatic breast cancer. *Methods*: This study included 16 patients with metastatic breast cancer and limited previous therapy for their metastatic disease. Mitoxantrone, 1.5 mg/m^2 per day, was given by continuous intravenous infusion for 14 consecutive days repeated every 21 days with concomitant granulocyte colony-stimulating factor support. Dose escalation was allowed. *Results*: No complete tumor response was seen. Two patients (13%, CI 0–29%) had a partial response, nine patients (56%) had progressive disease and the remaining five patients (31%) had stable disease on therapy. The major dose-limiting side effect was myelotoxicity. Two of the 16 patients (13%) experienced asymptomatic cardiotoxicity that required discontinuation of therapy. *Conclusions*: Our results indicate limited antitumor activity and significant toxicity of mitoxantrone given by continuous infusion as second-line chemotherapy for metastatic breast cancer. The objective response rate documented in this study is inferior to response rates reported with other second-line regimens, particularly the taxanes, now available for this patient population.

Key words Metastatic breast cancer · Continuous intravenous mitoxantrone · Chemotherapy schedule

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Introduction

Combination chemotherapy is currently the most efficacious treatment for metastatic carcinoma of the breast. Programs combining cyclophosphamide, 5-fluorouracil and either doxorubicin or methotrexate produce objective response rates in 50–70% of patients, including complete response rates close to 20% [1]. Although remissions have become commonplace in the treatment of metastatic breast cancer, the median duration of remissions induced by front-line combination chemotherapy is 6–15 months, and the median duration of survival is around 24 months [2]. Several chemotherapeutic agents have been used, either alone or in combination, in an attempt to reinduce remissions in patients with unsuccessful initial chemotherapy [3]. In the past few years, taxanes have emerged as effective second-line therapy for patients not helped by doxorubicin-based combinations [4]. The response rates and duration of response produced by second-line regimens, including paclitaxel, are considerably lower than those seen with first-line chemotherapy. There continues to be a need to explore further therapeutic options for patients with progressive metastatic disease who retain a good performance status and wish to pursue further therapy.

Mitoxantrone is an anthraquinone whose chemical structure suggested similar efficacy to, but less cardiotoxicity than, doxorubicin due to the lack of a daunosamine group on the molecule [5, 6]. Early phase II evaluation of mitoxantrone indicated objective response rates of 17–36% in patients with metastatic breast cancer [7–12]. Most of these studies used single daily doses ranging from 10 to 15 mg/m^2 given as an intravenous bolus every 3 to 4 weeks. In vitro studies have indicated

a very steep dose-response curve for mitoxantrone in breast cancer cell lines [13]. Attempts to escalate the dose of mitoxantrone, given as an intravenous bolus, to take advantage of the steep dose-response curve observed in vitro have been associated with unacceptable toxicity, and have not increased either the number of complete remissions or the duration of remission [14, 15]. The major dose-limiting side effects of mitoxantrone in these studies were cumulative myelotoxicity and to a lesser extent cardiotoxicity. Delivering doxorubicin as a continuous infusion substantially reduces peak plasma levels and markedly lessens the cardiotoxicity of the drug without any loss of its antitumor activity [16]. In vitro studies have demonstrated that increased duration of exposure to mitoxantrone produces an increased cytotoxic effect on cancer cells [17]. Based on the experience with continuous infusion doxorubicin and the promising preclinical data suggesting increased antitumor activity with prolonged exposure to mitoxantrone, the administration of mitoxantrone by continuous infusion has been studied in an attempt to reduce toxicity and optimize tumor response.

The first study of continuously infused mitoxantrone (2 mg over 24 h for 14 days) for treatment of breast cancer suggested a 70% objective response rate, but the data were published only in abstract form [18]. Subsequently, two small studies explored this schedule further. Mulder et al. reported a pilot study of ten patients with metastatic breast cancer without prior therapy for their metastatic disease who were treated with mitoxantrone 1.1 mg/m^2 daily for 2 weeks repeated every 4 weeks for a total of four cycles [19]. Two patients had complete remissions, four had partial remissions, and an additional four patients experienced stable disease. Kreisle et al. reported the results of another phase I study of 14-day continuous infusion of mitoxantrone in 16 patients with various advanced solid tumors excluding breast cancer [20]. This dose-finding study investigated three different dose levels of 1.0, 1.25, 1.5 mg/m^2 per day; the maximum tolerated dose was 1.5 mg/m^2 per day. The dose-limiting toxicity was grade 3 or 4 leukopenia. On the basis of the above results, we initiated a phase II study to determine the antitumor activity and toxicity of single-agent mitoxantrone administered at the maximally tolerated dose by continuous infusion with concomitant granulocyte colony-stimulating factor support in patients with metastatic breast cancer and limited prior therapy.

Patients and methods

Patient population

This study included 16 patients with metastatic breast cancer treated at the University of Texas MD Anderson Cancer Center between June 1991 and July 1993. Patients were eligible for the study if they had histologic proof of advanced breast cancer, estimated life expectancy greater than 12 weeks, performance status less than or equal to Zubrod scale 2, had measurable disease, and demonstrated adequate bone marrow (neutrophils $>1500/mm^3$, platelets $>100\,000/mm^3$), kidney (creatinine <2 mg/dl), liver (bilirubin <2 mg/dl), and cardiac reserves (left ventricular ejection fraction $>65\%$ or cardiac biopsy score <1). Patients could have received no more than one chemotherapeutic regimen for metastatic disease. Patients who had previously received mitoxantrone or high-dose chemotherapy with stem cell transplant were not eligible for this study. All patients gave written informed consent for the study.

Patient characteristics are summarized in Table 1. All patients suffered from progressive disease at the time of entry into the study, the median age was 48 years, and the median disease-free interval before relapse was 28 months. The majority of patients (75%) had visceral disease with a median of two involved sites, and 12 patients (75%) had received prior doxorubicin-based combination chemotherapy, 5 for metastatic disease and 7 as adjuvant therapy. Out of the 5 patients who had received doxorubicin for metastatic disease, 2 were considered doxorubicin-resistant at the time of entry into the study (progression on therapy or relapse within 6 months). Only one patient had received paclitaxel for metastatic disease before entering the study.

Pretreatment and response evaluation

Before entry all patients were evaluated for extent of disease. The evaluation included a clinical history, physical examination, blood chemistry, blood counts, electrocardiogram and resting echocardiogram or MUGA scan. For patients who had received >450 mg/m^2 doxorubicin by bolus injection or >600 mg/m^2 by 48- to 72-h continuous infusion, a cardiac biopsy was considered. Baseline imaging studies included a chest radiograph, bone scan, and computed tomography scan of the appropriate body cavities to establish the extent of disease. During therapy, relevant interim history was recorded, physical examination was performed and toxicity was evaluated before each course. Each patient was followed at least weekly with complete blood counts, and a chemistry panel was repeated at least once during every treatment course. Radiologic studies were repeated every second course. Monitoring of cardiac toxicity was as follows: Echocardiogram or MUGA scan was repeated after every two courses of therapy. If at any point during therapy the LVEF dropped below 50%, mitoxantrone was stopped. If the LVEF was between 50% and 65% and further

Table 1 Patient characteristics

Total number	16 (100%)
Age (years)	
Median	48
Range	29–81
Performance status (Zubrod)	
1	14 (87%)
2	1 (6%)
3	1 (6%)
Previous therapy	
Chemotherapy	14 (87%)
Hormonal	10 (62%)
Immunotherapy	2 (12%)
Radiation	7 (44%)
Number of prior chemotherapy regimens	
0	2 (12%)
1	10 (62%)
2	4 (25%)
Dominant disease sites	
Bone	5 (31%)
Visceral	12 (75%)
Node/soft tissue	11 (69%)
Number of sites involved	
1	4 (25%)
2	10 (62%)
3	2 (12%)

therapy would likely benefit a patient, endomyocardial biopsy was recommended. Cardiac biopsies were scored by the modified Billingham method [21]. If a biopsy grade <1 was obtained, mitoxantrone was continued and the LVEF was assessed before each subsequent course. If the biopsy grade was ≥ 1, mitoxantrone was discontinued.

Assessment of toxicity was based on the common toxicity criteria and grading system established by the National Cancer Institute. All patients who completed two courses of therapy were considered evaluable for both toxicity and tumor response. Tumor response was determined after each course of therapy. A complete response (CR) was defined as disappearance of all evidence of tumor for at least 4 weeks, a partial response (PR) as at least a 50% reduction in the sum of the products of the two longest diameters of measurable lesions for at least 4 weeks, and stable disease (SD) as no change in measurable lesions and no new lesions or progressive symptoms. Progressive disease was defined as the appearance of new lesions or an increase of more than 50% in the sum of the products of the diameters of any measurable lesion. Duration of response was measured from initiation of therapy until tumor progression.

Treatment regimen

Mitoxantrone was given by continuous infusion for 14 consecutive days using an outpatient infusion pump and a central venous catheter. The starting dose (level 0) was 1.5 mg/m^2 per day. If no toxicity greater than grade 1 was seen, the dose of mitoxantrone was escalated for the next course to 1.7 mg/m^2 per day (dose level $+1$). If the platelet count dropped below 50 000/mm^3 or granulocyte count fell below 1000/mm^3 with concomitant fever during therapy, the infusion was discontinued and the next dose was reduced to 1.25 mg/m^2 per day (dose level -1). Further dose reduction to 1.1 mg/m^2 per day (dose level -2) was allowed if significant toxicity was observed at dose level -1. All patients received granulocyte colony-stimulating factor support (G-CSF) at a dose of 5 μg/m^2 subcutaneously on days 15 through 19, or as long as necessary to reach an absolute granulocyte count >1500/mm^3. Treatments were repeated every 21 days or when the granulocyte count had recovered to >1500/mm^3 and the platelet count to $>100\,000$/mm^3. Therapy was continued for at least two courses unless there was evidence of rapidly progressing disease. If an objective response was seen, treatment was continued for 6 months beyond the maximal response. Patients could be withdrawn from study at any time by their expressed wish, or if significant toxicity, defined as unpredictable, irreversible, or grade 4, was observed. Patients who experienced progressive disease after two courses of therapy were also removed from the study.

Statistical design

This was a nonrandomized phase II trial conducted in two stages using the Simon design [22]. Type I and type II errors of 10% were accepted, and a $<10\%$ objective response rate was deemed of no clinical interest, whereas $>30\%$ response rates would be of clinical value. Accordingly, 12 patients were entered into the first stage, and if a response rate $>8.5\%$ was observed, then accrual was to continue to a total of 35 patients. The study was terminated after accrual of 16 patients owing to excess cardiotoxicity of 13%. With this accrual, the observed 13% objective response rate has a 95% confidence interval ranging from 0 to 29%.

Results

Tumor response

All patients were evaluable for tumor response and toxicity (Table 2). No CR was observed. Two patients (13%) experienced a PR lasting for 10 and 15 months, respectively. One of the patients with a PR had lung and bone involvement, and the other had liver and subdiaphragmatic lymph node metastases. For both patients, mitoxantrone was the first chemotherapy agent they had received for metastatic disease, but both had received prior tamoxifen, and one of them had also received vincristine, doxorubicin, cyclophosphamide and prednisone as adjuvant chemotherapy. Five patients (31%) had SD with a median duration of 6 months (range 3–9 months). Three of the five patients with SD experienced a less than 50% reduction in tumor size, while the other two patients had no change in tumor volume. Interestingly, one of the patients with SD had progressive disease while receiving doxorubicin-containing combination chemotherapy immediately before entry to the study and was therefore considered doxorubicin-resistant. The remaining nine patients in the study (56%) had tumor progression during the first two courses of therapy, and were considered resistant to mitoxantrone.

Table 2 Tumor response

Complete response	0 (0%)
Partial response	2 (13%)
Stable disease	5 (31%)
Progression	8 (50%)

Dose intensities expressed as mg/m^2 per week for each patient who received at least two courses of mitoxantrone are shown in Table 3. Table 3 also illustrates that even the initial level 0 dose intensity could not be maintained for most patients beyond the first two cycles.

Toxicity

All 16 patients evaluated for tumor response were also evaluated for toxicity. No death due to toxic effects occurred. A total of 58 courses were administered. The median number of courses per patient was two (range one to nine). A total of 35 courses were given at dose level 0 (1.5 mg/m^2 per day). At this dose level, the median granulocyte nadir was 400/mm^3 (range 0.0–4200/mm^3) observed at a median of 19 days after starting therapy, and the median platelet nadir was 125 000/mm^3 (range 13 000–241 000/mm^3) at a median of 22 days after therapy. The median treatment interval was 29 days (range 23–64 days). One patient tolerated a dose increase, and received a total of three courses at dose level $+1$ (1.7 mg/m^2 per day). Dose reduction was necessary in nine patients (60%). A total of 19 courses were given at dose level -1 (1.25 mg/m^2 per day), and two courses at dose level -2 (1.1 mg/m^2 per day). The most common reasons for dose reduction were grade 3–4 granulocytopenia alone or in combination with thrombocytopenia, mucositis and fever. Dose reduction was necessary for isolated thrombocytopenia on two occasions. Table 4 presents the reasons for dose reduction by course. Four episodes of neutropenic fever were recorded during the study and two patients required

Table 3 Dose intensity (mg/m^2 per week) by course by patient. One patient received only one course of therapy due to rapidly progressive disease; dose intensity for this patient is not included in the table

Patient no.	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	4.3	4.08	3.85						
2	5.45	3.13	2.37	3.6	2.27	2.85			
3	3.97	5.57	3.82	2.22	5.57				
4	6.40	5.07							
5	5.07	5.07	4.75	3.77	3.07	4.54	3.14	2.55	1.38
6	4.32	4.32							
7	5.07	5.78							
8	4.32	7.23							
9	5.29	7.39							
10	5.25	5.74	4.39	5.25	5.25	5.25	3.28		
11	2.29	3.19							
12	5.25	5.45	4.90	4.45	2.49	2.85			
13	2.67	3.5							
14	4.32	2.4							
15	5.07	3.58	4.39	4.25	1.87				
16	5.25								

Table 4 Reasons for dose reduction by course (*inf* neutropenic infection or fever, *anc* granulocytopenia, *plt* thrombocytopenia, *st* stomatitis)

Course no.	No. of patients receiving treatment	No. of patients at dose level				Reasons for reduction
		+1	0	−1	−2	
1	16	0	16	0	0	
2	15	1	9	5	0	anc/st, inf/st, inf, inf, anc
3	7	1	3	2	1	anc
4	6	1	2	3	0	anc/plt
5	6	0	2	4	0	plt, inf
6	4	0	1	3	0	plt/st
7	2	0	1	1	0	
8	2	0	1	1	0	
9	1	0	0	0	1	plt

hospitalization for neutropenic fever. Two patients experienced a platelet nadir below 20 000/mm^3 without any clinical episode of bleeding. One patient required red cell transfusion for a hematocrit of 22.6%.

For two patients (13%) dose reduction was necessary for declining cardiac function. Both of these patients remained asymptomatic for heart failure and declining LVEF was detected on routine echocardiograms after courses 8 and 9, respectively. They had received total cumulative doses of mitoxantrone of 169 and 176 mg/m^2, respectively. One of the patients had received doxorubicin (cumulative dose of 400 mg/m^2 given by 48-h infusions) before entering the study; no other risk factors for cardiotoxicity were identified. Both patients underwent cardiac biopsy and the biopsy scores indicated grade 1 cardiomyopathy, which prompted discontinuation of mitoxantrone therapy. Eight other patients who received total cumulative doses of mitoxantrone ranging from 38.5 to 122 mg/m^2 and had follow-up echocardiograms experienced no decline in their LVEF. Five of these eight patients had received doxorubicin before.

Nonhematologic toxic effects were generally mild: grade 2 or greater mucositis, nausea and diarrhea affected 66%, 40% and 26% of patients, respectively.

Discussion

Mitoxantrone is an anthracene analogue with antitumor activity [5]. A number of early phase II trials suggested that mitoxantrone may be as active as doxorubicin with fewer side effects, particularly cardiotoxicity. Several phase I and II studies have evaluated the efficacy of rapid intravenous bolus mitoxantrone as a single agent for metastatic breast cancer and have demonstrated objective response rates ranging from 17% to 39% [6–12]. Preclinical studies indicated a steep dose-response curve, and suggested that continuous infusion may be the optimal way to administer this drug in order to achieve maximal cytotoxic effect with minimal toxicity. Two small studies, one reported as an abstract and the other as a letter, indicated 70% and 60% objective response rates in metastatic breast cancer, respectively, when mitoxantrone was administered as continuous intravenous infusion [20, 21]. On the basis of these encouraging data, we initiated a phase II study to evaluate the efficacy and side effects of maximally tolerated continuous infusion mitoxantrone in patients with metastatic breast cancer and limited prior therapy. Our starting dose was 1.5 mg/m^2 per day which was the previously suggested

maximally tolerated dose for continuous administration [21]; however, in this study dose escalation was allowed with concomitant G-CSF support.

Our results confirm that the maximally tolerated dose is around 1.5 mg/m^2 per day when given by 14-day continuous infusion. Only 1 out of 16 patients tolerated a dose increase for a limited period of time. In fact, for most patients even the starting dose level could not be maintained beyond two or three cycles because of toxicity (Table 3). The toxicity profile of mitoxantrone in this study was similar to that previously reported [23]. The major dose-limiting side effect was myelotoxicity. In this study, no significant dose escalation could be achieved even with concomitant hematopoietic growth factor support. However, G-CSF was started on day 15 after initiation of continuous infusion therapy and this may be regarded as suboptimal scheduling since the median granulocyte nadir was observed on day 19. G-CSF might have been more effective to support bone marrow recovery if started within the first few days of infusion. However, the optimal schedule for administration of G-CSF with prolonged continuous infusion chemotherapy is unknown. While administration late in the course may not influence the nadir or shorten recovery significantly as our experience suggests, early support with hematopoietic growth factors administered concomitantly with cytotoxic therapy could paradoxically worsen neutropenia owing to its recruiting effect on resting hematopoietic stem cells.

A surprisingly high number of patients, 2 out of 16, experienced asymptomatic cardiotoxicity that required dose reduction and discontinuation of therapy. Both patients had received relatively high cumulative doses of mitoxantrone (169 and 176 mg/m^2) but had no other risk factors for cardiac toxicity such as mediastinal radiation, coronary artery disease or high blood pressure. One of the patients had received a total of 400 mg/m^2 of doxorubicin given by 48-h infusions before entering the study. Both patients had follow-up MUGA scans after completion of mitoxantrone at 7 and 10 months, respectively, which indicated improvement in LVEF for one patient and return of left ventricular function to pretreatment level for the other, suggesting that the cardiotoxic effect was reversible. In patients previously unexposed to anthracyclines the risk of cardiotoxicity is less than 5% at cumulated doses <160 mg/m^2 of mitoxantrone [24]. However, for patients who have received doxorubicin previously (median cumulative dose 239 mg/m^2) the risk of cardiotoxicity starts to rise when the cumulative mitoxantrone dose reaches about 100 mg/m^2 [24]. The high total cumulative doses of mitoxantrone, 169 mg/m^2 and 176 mg/m^2 received by our two patients could explain the excess cardiotoxicity observed in this study.

No CR was seen; 13% of the patients had a PR, and 53% experienced progression of their disease. These results, although with a wide confidence interval due to the small size of the study, are considerably worse than those reported for the two small pilot studies of previously untreated patients with metastatic breast cancer. It is of note that in our study the majority of the patients had received one chemotherapy regimen before starting mitoxantrone, 75% had received prior doxorubicin-based combination chemotherapy, and two were considered doxorubicin-resistant at the time of entry to the study. This may have contributed to the disappointingly low response rates seen in our study. Our data indicate limited antitumor activity at the cost of significant myelotoxicity and cardiotoxicity. The objective response rate achieved by mitoxantrone in this study is inferior to response rates reported with other second-line regimens, particularly the taxanes, now available for this patient population [25].

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