The Use of Mitoxantrone Plus Cyclophosphamide as First-Line Treatment of Metastatic Breast Cancer

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Thirty-two patients with metastatic breast cancer who had not received prior chemotherapy for metastatic disease were entered into a trial of mitoxantrone 12 mg/m^2 plus cyclophosphamide 600 mg/m^2 given at three weekly intervals. Thirty-one patients are eligible for assessment. Response was seen in 65% (4/31 complete regression; 16/31 partial regression). Median duration of response was 6 months and median duration of survival was 10 months. Mitoxantrone + cyclophosphamide appears to be an active combination in treatment of metastatic breast cancer.

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MITOXANTRONE (dihydroxyanthracenedione dihydrochloride), a new anthraquinone compound,[1] has demonstrated marked antitumor activity in experimental tumor systems and has also been tested in a number of phase II studies[2–4] in patients with metastatic breast cancer. The response rate has generally been of the order of 20% to 30% in previously treated patients thus establishing this drug as an active agent for the treatment of this disease. A favorable feature of therapy with mitoxantrone is the relatively low toxicity, particularly in regard to nausea and vomiting, alopecia, and cardiac toxicity. In a previous study from this unit we reported the results of a combination regimen including mitoxantrone, methotrexate, and 5-fluorouracil given as first-line chemotherapy in patients with metastatic breast cancer. This regimen was designed in an attempt to retain the desirable toxicity profile while yet increasing the response rate. In the event, the results of that study were somewhat disappointing with no evidence of synergism between the chemotherapeutic drugs used. In the current study mitoxantrone has been combined with cyclophosphamide in an attempt to increase both the response rate and response duration.

Patients and Methods

Thirty-two patients attending the Breast Clinic of the Johannesburg Hospital were entered into the study between February 1984 and March 1985. The study was analyzed in July 1985. All subjects were women who had progressive symptomatic, locally advanced or metastatic breast cancer and all had at least one area of measurable disease. Patients who had received previous chemotherapy for advanced disease or adjuvant chemotherapy within the last 2 years were not eligible for study. Before starting therapy all patients had a leukocyte count $> 4.0 \times 10^3/mm^3$, platelets $> 1 \times 10^5/mm^3$, and bilirubin and creatinine values < 2.0 mg%. Further patient details are shown in Table 1.

Pretreatment investigations included chest x-ray, radioisotope bone and liver scans, full blood count and platelets, biochemistry profile including renal and hepatic function tests, electrocardiogram (ECG), and a baseline, resting, multiple gated equilibrium blood pool imaging (MUGA) scan. Other investigations were performed as indicated. Suspected hepatic metastases were confirmed by means of computerized tomography. Performance status was recorded using Eastern Cooperative Oncology Group (ECOG) criteria. The chemotherapy regimen consisted of mitoxantrone 12 mg/m^2 intravenously (IV) administered over 30 minutes followed by cyclophosphamide 600 mg/m^2 IV also over 30 minutes, both drugs being given three times weekly. Hematologic toxicity was assessed at 3 weeks and the hematologic values determined the retreatment schedule. If at 3 weeks leukocyte count was >3.5 and platelets were $>1 \times 10^5/mm^3$ retreatment was with 100% doses of both drugs. If hematologic depression was still present at 3 weeks, therapy was delayed until leukocyte count was >2.0 and platelets were $>7 \times 10^4/mm^3$ and therapy was then recommenced at 50% of dose levels for both drugs. Therapy was planned to a total of 12 courses or progression, whichever was sooner. Patients who were still responding after 12 cycles were followed up with no further therapy. No dosage escalation was planned.

Re-evaluation included three-weekly physical examination, weekly blood count and blood chemistry, six-weekly chest x-ray, and three-monthly scans where these were initially involved. Response of hepatic metastases was assessed by means of computerized tomography.

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TABLE 1. Characteristics of Patients Entered Into Study of Mitoxantrone + Cyclophosphamide as First-Line Treatment for Metastatic Breast Cancer

Age (yr)	
Mean	52.7
Median	43.5
No. of metastatic sites	
Mean	1.6
Median	1.0
Menstrual status	
Premenopausal	9
Postmenopausal	23
Estrogen receptor status	
ER positive	0
ER negative	11
ER unknown	22
Tumor-free interval (mo)	
Median	38
Adjuvant chemotherapy (CMF)	4
Prior hormone treatment	9
Responsive	5

ER: estrogen receptor.

Cardiac status was reassessed using repeat ECG and follow-up MUGA scans at the end of therapy or whenever indicated on clinical grounds. Assessment of response was according to ECOG criteria[5] and included the categories CR (disappearance of all evidence of clinically active tumor for a minimum of 4 weeks), PR (partial regression consisting of >50% decrease in the sum of the products of all diameters of measurable lesions for a minimum of 4 weeks), and SD (stationary status of disease less than partial remission for a minimum of 4 weeks with no evidence of progression of any lesion). Duration of response was measured from the date of initiation of therapy to any evidence of progression. An adequate trial of treatment was defined as two cycles of chemotherapy. Those patients with either CR, PR, or SD continued on the same treatment for as long as response was maintained or to a total of 12 cycles. Patients who showed progression, either after the initial two cycles or at any time thereafter were removed from study but continue to be followed-up for assessment of survival.

TABLE 2. Response to Mitoxantrone + Cyclophosphamide in Metastatic Breast Cancer by Site

Site	No. involved	CR	PR	SD
Node and soft tissue	14	2	8	3
Lung and pleura	14	2	8	3
Bone	10	0	6	1
Liver	6	0	2	2
Other	3	0	2	1

CR: complete regression; PR: partial regression; SD: stationary status of disease.

Second-line treatment consisted of vindesine 3 mg/m^2 and 4'epiadriamycin 60 mg/m^2 for all patients with progressive disease who were eligible for second-line treatment protocols. Eligibility criteria for second-line treatment included documented evidence of progression on cyclophosphamide-mitoxantrone, performance status 1 or 2 (ECOG) and MUGA > 48%. Statistical analysis of survival was by means of the log-rank test.[6] Toxicity assessment was by means of World Health Organization (WHO) criteria.[7]

All patients gave informed consent and the study was approved by The Committee on Ethics of Human Experimentation of the Faculty of Medicine, University of the Witwatersrand.

Results

Of the 32 patients entered into the study, 31 were eligible for assessment of response. One patient died of neutropenic sepsis after the first cycle of treatment and thus is not included in the assessment of response but is included in the toxicity analysis. Median number of treatment cycles at the time of analysis was 3.5 (mean, 5.4 cycles). The overall response rate (CR: 4/31, 13%; PR: 16/31, 52%) was 65% with a further seven patients having disease stabilization for at least 4 weeks. Responses (Table 2) were seen at all disease sites including bone and liver involvement. The median duration of response was 6 months and the median duration of survival of the entire group was 10 months (Fig. 1). The four patients who achieved complete remission did so after a median of three treatment cycles. Two of these patients are still receiving chemotherapy while the other two have received 12 cycles of treatment and are being followed-up with no further treatment at 10+ and 11+ months, respectively. Of the 31 patients entered on the trial, 16 are still alive (two CR on no therapy; two CR and seven PR or SD patients still receiving mitoxantrone + cyclophosphamide; five patients receiving second-line treatment). Altogether, 17 patients went on to receive the second-line chemotherapy regimen. Response to second-line treatment has been observed in 6/17 (35%) patients, including 4 who were initially responsive to mitoxantrone plus cyclophosphamide and 2 who were nonresponsive to this combination.

Toxicity (Table 3) consisted predominantly of reversible depression of the leukocyte count and to a lesser extent of hemoglobin concentration and platelet count. Most hematologic toxicity occurred between 7 and 14 days after therapy and had recovered by the third week. One patient developed severe hematologic toxicity (leukocyte count $0.7 \times 10^3/mm^3$) after the first cycle of chemotherapy and died of neutropenic infection. Although this patient had bilirubin values <2 mg% at initial evaluation, extensive hepatic involvement was present, which may have altered

drug metabolism. In the other patients hematologic depression > grade 2 was rare and the fall in leukocyte count was transient. The majority of treatment cycles were given at three-weekly intervals as planned and without dose reduction. Although it appears from Table 3 that cumulative hematologic toxicity may have occurred, the small number of patients receiving 10 or more cycles of chemotherapy makes statistical interpretation difficult. Severe nausea/vomiting was infrequent. Ten patients reported neither nausea nor vomiting with any treatment cycle. Alopecia when it occurred (40%) was usually mild to moderate and patchy (grade 1 or 2 severity). Cardiac toxicity was not encountered in this study with doses of up to 144 mg/m^2.

Discussion

The current study evaluates the efficacy and safety of mitoxantrone + cyclophosphamide as first-line chemotherapy in patients with advanced breast cancer and compares the results of this regimen with the results seen in a similar group of patients treated with a combination of mitoxantrone, methotrexate, and 5-fluorouracil. Although the two studies were sequential, the patient populations had similar characteristics, were treated in the same unit, and the two studies were carried out within a short period and with similar dosage of mitoxantrone. It thus appears reasonable to compare the two investigations and furthermore to relate this data to other investigations published in the literature. In the current study the objective response rate to mitoxantrone + cyclophosphamide was 65% and this appears to be considerably better than the results obtained with cyclophosphamide alone (average, 34%),[8] with mitoxantrone alone (range, 26%–44%)[9-11] or with the previously tested combination of mitoxantrone, methotrexate, and 5-fluorouracil (38%).[4] With an objective response rate of 20/31 (65%) patients, the true response rate to the mitoxantrone + cyclophosphamide appears to be in excess of 50% with a probability of only 0.05 of α or β error.[12] In addition, complete responses were seen in four patients and these patients had the longest duration of response and survival. However, the median duration of response was only 6 months and this figure appears to be somewhat low for first-line combination chemotherapy regimens.[13-15] No obvious reason could be found to account for this discrepancy. In view of these results it is justifiable to ask what the response to second-line therapy and the overall survival is like in pa-

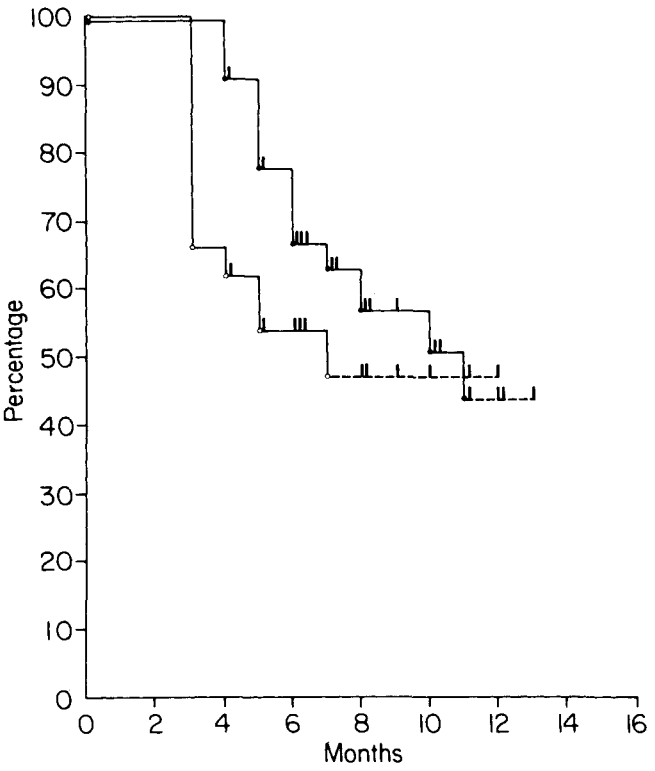

FIG. 1. Cumulative duration of response (○) and survival (●) of patients with advanced breast cancer treated with mitoxantrone + cyclophosphamide as first-line chemotherapy.

TABLE 3. Toxicity: Mitoxantrone + Cyclophosphamide in Advanced Breast Cancer

Course no.	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
No. of patients receiving this course		32	31	28	22	16	13	12	6	5	5	4	3
Cumulative median nadir values													
Hemoglobin (g/dl)	13.26	12.6	12.5	10.4	10.1	13.0	13.0	11.7	11.7	11.7	11.1	10.6	10.3
Granulocyte count ($\times 10^3$/mm^3)	2.3	1.8	1.7	1.8	1.7	1.0	1.1	1.2	1.6	1.3	1.0	2.2	1.7
Platelets ($\times 10^5$/mm^3)	255	187	193	193	185	167	125	133	178	153	103	101	103
Nausea/vomiting (grade)		1	1	1	1	1	1	1	1	1	1	1	1
Alopecia (grade)		0	0	0	0	0	1	1	1	1	1	1	1
Percentage of planned chemotherapy administered		100	100	100	80	80	100	100	100	100	70	100	80

tients treated with this combination as initial chemotherapy. To assess this a standardized second-line chemotherapy regimen was employed. In this regard the combination of mitoxantrone plus cyclophosphamide generally has been fairly safe to administer and with no long-term toxicity. Second-line treatment with an anthracycline-containing regimen was possible in the majority of patients requiring such therapy, and the response to second-line treatment does not appear to have been compromized. Further investigations will be necessary to determine whether other combinations including mitoxantrone and/or alterations in drug scheduling will allow for a significantly higher complete remission rate and more prolonged duration of response.

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