Mitoxantrone, Methotrexate, and 5-Fluorouracil Combination Chemotherapy as First-Line Treatment in Stage IV Breast Cancer

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Fifty patients with Stage IV breast cancer were entered into a prospective Phase II trial of combination chemotherapy that consisted of mitoxantrone (10 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2) given in a 3-weekly schedule. Objective response to treatment was seen in 18 of 48 assessable patients (38%). Responses were seen predominantly in the lung and pleura and the node and soft tissue sites of disease. The median duration of response was 7 months. Toxicity from treatment consisted predominantly of reversible leukopenia. Other toxicities such as nausea and alopecia occurred in less than one half of the patients in the study group. The combination was well-tolerated, and appears to be moderately effective.

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MITOXANTRONE (dihydroxyanthracenedione dihydrochloride),[1] a new anthraquinone compound, has demonstrated marked antitumour activity in a number of experimental systems[2,3] and has also been tested in a number of Phase II studies in patients with metastatic breast cancer.[4,5] Potential advantages of this new agent include an apparently lower incidence of cardiotoxicity than that encountered with the use of the anthracycline antitumour antibiotics and suggestive evidence that nausea and alopecia may also be less frequently encountered. There is, however, only limited information on the use of this agent in combination therapy. The current study was undertaken to determine the response rate, duration of response, and quality of life for patients with breast cancer with the use of a combination regimen consisting of mitoxantrone, methotrexate, and 5-fluorouracil as first-line treatment for metastatic disease.

Materials and Methods

Fifty patients who were being treated at the Breast Clinic of the Johannesburg Hospital were entered into the study between February 1983 and January 1984. Patient details are shown in Table 1. All had Stage IV breast cancer with at least one area of measurable disease and a performance status of better than or equal to Karnofsky score of 50 to 60. None had received prior chemotherapy for metastatic breast cancer, although six patients had received adjuvant CMF chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) and 27 patients had received a trial of hormone treatment for metastatic breast cancer. These latter patients showed clear evience of progression or metastasis, and hormonal treatment was discontinued for at least 4 weeks before they were entered onto the study. Other entry criteria included informed consent; the presence of normal pretreatment hematologic, liver, and renal function values; and no prior history of cardiac disease. The chemotherapy regimen consisted of mitoxantrone 10 mg/m^2 intravenously day 1, methotrexate 40 mg/m^2 intravenously day 1, and 5-fluorouracil 600 mg/m^2 intravenously day 1 (NMF therapy). The first three patients entered onto the study received, in addition, methotrexate 40 mg/m^2 intravenously day 8 and 5-fluorouracil 600 mg/m^2 intravenously day 8 with the first course, but because of excessive hematologic toxicity the day 8 dose was omitted with subsequent courses and patients. Dose modification for hemopoetic toxicity was based on nadir counts during previous treatment courses and included either a 20% or 40% reduction of mitoxantrone dose, depending on the degree of hematologic depression (leukocyte count 1000–2000 μl and/or platelet count 50,000–100,000 μl, 20% dose reduction; leukocyte count < 1000 μl and/or platelet count < 50,000 μl, 40% dose reduction). The treatment protocol also allowed for dosage escalation (20% increase of mitoxantrone dose) for patients who had minimal

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TABLE 1. Characteristics of Patients Entered Into the Trial of Mitoxantrone, Methotrexate, and 5-Fluorouracil in Metastatic Breast Cancer

Age (yr)	
Median	57.5
Range	52.3–61.1
Mean	54.5
No. of metastatic sites	
Mean	1.9
Median	2.0
Range	1–3
Menstrual status (no.)	
Premenopausal	9
Postmenopausal	41
ER status (no.)	
ER-positive	5
ER-negative	9
ER-unknown	36
Tumor-free interval (mo) (median)	29
Adjuvant chemotherapy (CMF) (no.)	6
Prior hormone treatment (no.)	27
Responsive	19
Nonresponsive	8

ER: estrogen receptor; CMF: cyclophosphamide; methotrexate, 5-fluorouracil.

hemopoetic toxicity. Pretreatment investigations included full physical examination, chest x-ray, bone and liver scans, abdominal ultrasound and/or computerized tomography, electrocardiogram (ECG) and cardiac function assessment by gated radionuclide cardiac ejection fraction, full blood count, and liver and renal function tests. Response to treatment and toxicity were assessed by International Union Against Cancer (UICC)[6] and World Health Organization (WHO)[7] criteria, respectively. An adequate trial for efficacy assessment was defined as at least two cycles of treatment. Patients who showed continuing response were treated for up to 12 months. Hematologic toxicity was monitored by means of weekly blood counts and cardiac function by means of ECG before each course of treatment and radionuclide ejection fraction with any change in cardiovascular status and when the patient was taken off study.

TABLE 2. Response According to Site of Disease

Site	No. involved	CR	PR	SD	Duration of responses (by site) (mo)
Node and soft tissue	46	4	12	9	7 (median) 3–9 (range)
Lung and pleura	14	3	3	4	6 (median) 2–10 (range)
Bone	14	0	2	3	6+, 4
Peripheral nerve	4	0	0	2	—
Liver	3	0	1	0	6
Bone marrow	3	0	1	2	7

CR: complete response; PR: partial response; SD: stable disease.

The study was approved by the Ethics Committee of the University of the Witwatersrand and the Medicine Control Council of South Africa.

Results

Forty-eight patients were eligible for assessment of response to treatment. Two patients refused further chemotherapy after the first course of treatment. The median number of treatment cycles for assessable patients was 4 (mean, 4.8). Overall response rate (complete response, 5/48; partial response, 13/48) was 38%, with a further 9 patients having disease stabilization for at least 2 months. Responses (Table 2) were seen predominantly in the lung and pleura (43%) and the node and soft tissue (35%) sites of disease, although one patient with bone marrow involvement showed partial clearing of the marrow infiltrate (to <5% involvement of marrow area on trephine biopsy together with a normocellular marrow and improvement in peripheral blood hematologic values, although residual foci of infiltration were still visible) and one of three patients with extensive hepatic involvement also showed a partial response to treatment.

The median duration of response was 7 months. Three patients who went into complete remission and who received 12 cycles of therapy continue to be followed in unmaintained remission. Six patients are currently still receiving chemotherapy (all >5 cycles). Sixteen patients have died (3 on study; 13 off study after disease progression). Patients who were withdrawn from the study because of disease progression were treated with a variety of other chemotherapeutic (vincristine + Adriamycin (doxorubicin), 17; high-dose cyclophosphamide, 5; mitomycin C + 5-fluorouracil, 5) and hormone (aminoglutethimide, 6; medroxyprogesterone acetate, 4) treatment regimens. Response to second chemotherapy occurred in 9 of 27 patients and to second hormone treatment in 2 of 10 patients. The median duration of survival of the patients entered onto the trial has not been reached, but will be in excess of 15 months.

Toxicity resulting from treatment is shown in Table 3. Hematologic toxicity generally consisted only of reversible depression of the leukocyte count. The nadir levels shown in Table 3 generally occurred 7 to 14 days after treatment, with recovery at 3 to 4 weeks after therapy. Depression of platelet count and hemoglobin levels occurred infrequently. There was no evidence of cumulative hematologic toxicity. Mild to moderate nausea occurred in 21 patients and with 87 of 233 treatment cycles. Severe nausea was encountered infrequently (21/233 treatment cycles). Only 27 patients experienced moderate to severe alopecia. Cardiac abnormalities developed in five patients during treatment. Three cardiac episodes were related to disease progression (malignant pericardial effusion). One

TABLE 3. Toxicity From Mitoxantrone, Methotrexate, and 5-Fluorouracil Chemotherapy Regimen

Cycle no.		1	2	3	4	5	6	7	8	9	10	11	12
No. of patients receiving this cycle		50	45	32	27	22	17	13	9	6	4	4	4
Cumulative mitoxantrone dose (mg/m^2)													
Mean		10	20.2	30.3	40.4	50.4	60.2	69.8	79.4	88.7	97.7	106.7	115.7
Median		10	20	30	40	50	60	70	80	90	100	110	120
	Pretreatment values	Nadir values											
Hb concentration g/dl													
Mean	13.5	12.6	12.4	12.1	12.1	11.6	12.0	11.4	11.3	11.7	12.1	11.3	11.6
Median	13.8	12.6	12.3	11.6	12.1	11.3	11.9	11.1	11.7	11.3	11.9	11.1	11.3
Granulocyte count $\times 10^3/mm^3$													
Mean	2.4	1.4	1.3	1.3	1.4	1.2	1.2	1.6	1.6	1.5	1.4	1.3	1.2
Median	2.2	1.4	1.3	1.4	1.2	1.2	1.1	1.4	1.2	1.0	1.5	1.3	1.2
Platelet count $\times 10^6 mm^3$													
Mean	260	189	191	177	180	154	176	186	180	168	144	148	177
Median	240	194	173	173	191	111	160	179	172	172	137	146	198
Cardiotoxicity													
No.			1		1								
Grade			2		1								91

patient was found to have an asymptomatic decrease in cardiac ejection fraction when coming off study because of disease progression (decrease from 69.1% to 57.0% in resting ejection fraction after receiving 40 mg/m^2 mitoxantrone), and one patient had clinical evidence of cardiac failure, which was ascribed to chemotherapy (fall in resting ejection fraction from 63.7% to 39.0% after the administration of 20 mg/m^2 mitoxantrone). In neither patient was any predisposing factor identified.

Discussion

In this study the response rate to mitoxantrone, methotrexate, and 5-fluorouracil (38%) was not significantly different from that reported for the use of mitoxantrone as single-agent treatment (range, 26%–44%).[8–10] This lack of synergy with the two other drugs used was somewhat disappointing, and a number of factors were considered to explain this finding. In regard to patient characteristics such as age, extent and distribution of metastases, and tumour-free interval, the study group in this investigation appeared comparable to those entered in other studies of chemotheray for metastatic breast cancer. Twenty-seven patients had received a trial of hormone therapy before starting chemotherapy. However, there is no evidence that a trial of hormone therapy diminishes the chance of response to chemotherapy. Only a minority of patients in this study had received adjuvant chemotherapy for Stage II breast cancer, which was also not a factor accounting for the relatively low response rate. The numbers are small; however, the six patients who had failed previous adjuvant CMF appeared to respond (3/6 partial responses) in equal measure to treatment with NMF for metastatic disease as those who had no prior exposure to chemotherapy. These findings are compatible with those reported by Rossi and co-workers,[11] who found that prior adjuvant chemotherapy with CMF did not compromise the response to treatment with the same regimen in those patients who failed adjuvant treatment.

Although combination chemotherapy has been reported to give response rates as high as 80%[12] in patients with metastatic breast cancer, the range of response has varied considerably. Equivalent three-drug combinations such as CMF have reported response rates varying from 40% to 70%.[13,14] Although the results of the current study are within the range reported for combination chemotherapy, it is possible that either one or both of the additional agents were, in fact, antagonistic, and further trials will have to be undertaken to determine the optimum combinations that contain mitoxantrone.

Although this study has not demonstrated any striking advantage of NMF chemotherapy in terms of response rate, the other aim of the study was to determine tolerability and quality of life. The NMF regimen was generally well-tolerated, and significant numbers of patients experienced either little or no nausea or alopecia. Significant cardiotoxicity due to treatment was seen in only two instances: one in a patient with an asymptomatic reduction in cardiac ejection fraction and one in a patient with mild evidence of cardiac failure, which was controlled with the

use of diuretics. Although hematologic toxicity was exaggerated by the addition of methotrexate and 5-fluorouracil on day 8 of the cycle, the 3-weekly schedule was generally well-tolerated by the majority of patients, with recovery of the leukocyte count generally occurring at 3 to 4 weeks. Further attention to scheduling and combination with different agents may well increase the efficacy while retaining tolerability, which is a prominent feature of treatment with mitoxantrone.

REFERENCES

1. Johnson RK, Broone MG, Howard WS. Experimental therapeutic and biochemical studies of anthracenedione derivatives (Abstr). In: Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, Brussels, Belgium, October 15–17, 1981.

2. Wallace RE, Murdock KC, Angier RB, Durr FE. Activity of a novel anthracenedione, 1,4-dihydroxy-5,8-bis((2-(2 hydromethyl)amino) ethyl)amino)-9,10-anthracenedione dihydrochloride, against experimental tumour in mice. *Cancer Res* 1979; 39:1570–1574.

3. Von Hoff DD, Coltman CA, Forseth B. Activity of mitoxantrone in a human tumour cloning system. *Cancer Res* 1981; 41:1853–1855.

4. Yap HY, Blumenschein GR, Schell FC, Buzdar AU, Valdevisio M, Bodey GP. Dihydroxyanthracenedione: A promising new drug in the treatment of metastatic breast cancer. *Ann Intern Med* 1981; 95:694–697.

5. Neidhart JA, Roach RW. A randomised study of mitoxantrone (M) and adriamycin (A) in breast cancer patients failing primary therapy. *Proc Am Soc Clin Oncol* 1982; 1:86.

6. Hayward JL, Rubens RD, Carbone PP, Heyson J-C, Kumaoka S, Segaloff A. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977; 35:292–298.

7. World Health Organization. (1979) WHO Handbook for Reporting Results of Cancer Treatment. WHO offset publication No. 48. Geneva: WHO.

8. Neidhart JA, Gochnour D, Roach RW, Steinberg JA, Young D. Mitoxantrone *versus* doxorubicin in advanced breast cancer: A randomised cross over trial. *Cancer Treat Rev* 1983; (Suppl) 10:41–46.

9. Smith IE, Stuart-Harris R, Pavlidis N, Bozek T. Mitoxantrone (Novantrone) as single agent and in combination chemotherapy in the treatment of advanced breast cancer. *Cancer Treat Rev* 1983; (Suppl) 10:37–40.

10. Mouridsen HT, Rose C, Nooy MA, van Oosterom AT. Mitoxantrone as first line cytotoxic therapy in advanced breast cancer: Preliminary results of a Phase II study. *Cancer Treat Rev* 1983; (Suppl) 10:47–52.

11. Rossi A, Tancini G, Marchini S, Bonnadonna G. Response to secondary treatment after surgical adjuvant CM ± for breast cancer. *Proc Am Assoc Cancer Res* 1980; 21:190.

12. Cooper RG. Combination chemotherapy in hormone resistant breast cancer. *Proc Am Assoc Cancer Res* 1969; 1:15.

13. Brambilla C, de Lena M, Rossi A, Valagussa P, Bonadonna G. Response and survival in advanced breast cancer after two non-cross resistant combinations. *Br Med J* 1976; 1:801–804.

14. Cannellos GP, de Vita VT, Gold RL, Chabner BA, Schein PS, Young RC. Cyclical combination chemotherapy for advanced breast carcinoma. *Br Med J* 1974; 1:218–220.