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Vincristine, doxorubicin and mitomycin (VAM) in patients with advanced breast cancer previously treated with cyclophosphamide, methotrexate and fluorouracil (CMF)

A clinical trial of the piedmont oncology association (POA)*

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Summary. *Thirty-six evaluable patients with advanced breast cancer who had failed prior CMF therapy [15 (42%) as adjuvant treatment and 21 (58%) for advanced disease] were treated with a combination of vincristine, doxorubicin, and mitomycin (VAM). There was one CR and 10 PR, giving a response rate of 31% (P, 95% confidence interval, 15%–47%). Response was not significantly related to age, performance status, disease-free interval, dominant site of disease, number of sites of disease, or estrogen receptor status. The median duration of response was 5 months for patients attaining CR or PR and 4.6 months for patients with stable disease. The median survival for patients with CR or PR of 7.9 months was not better than for those with stable disease (8.0 months), but both groups had significantly longer survival than those with initial progression. Patients who received VAM after failing adjuvant CMF had a 53% response rate (8 of 15), as against a 14% response rate (3 of 21) in those failing CMF for advanced disease ($P < 0.05$). In spite of this difference, the survival distributions for these two groups were not significantly different. Myelosuppression was moderate and no cardiac toxicity was seen. The addition of mitomycin to vincristine and doxorubicin in previously treated patients does not appear to improve the results obtained with vincristine and doxorubicin alone.*

Introduction

Metastatic breast cancer remains one of the most formidable challenges of modern cancer chemotherapy. Although first-line treatment programs are commonly associated with response rates of 50%–80%, responses are usually partial and of brief duration; rarely are patients cured. The results of second-line treatment with chemotherapy are relatively poor, with 20%–40% of patients responding, usually for only several months. The combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) is one of the most widely used chemotherapeutic regimens for breast cancer. CMF has been used extensively both in the preventive (adjuvant) setting and in patients with advanced disease. The development of an effective second-line treatment program for patients failing the CMF regimen was the main objective of this study.

Doxorubicin (adriamycin) remains one of the most active drugs in the treatment of breast cancer. Response rates of 16%–63% have been noted with doxorubicin used as a single agent in breast cancer patients without prior treatment. In previously treated patients an 11%–33% response rate has been demonstrated [10]. Vincristine has been demonstrated to have a 20% response rate when used as a single agent [13]. Vincristine is an attractive drug to use in combination regimens for breast cancer, since it is not associated with substantial myelosuppression and has a different mechanism of action than most other commonly used agents. The combination of vincristine and doxorubicin has previously been shown by Brambilla and associates to produce responses of 35% in patients who developed progression or relapse following treatment with CMF [1].

Mitomycin has also been shown to have substantial activity in patients with advanced breast cancer. In two reviews a 24% partial and a 35% overall response rate were noted when mitomycin was used as a single agent [2, 10]. Godfrey and colleagues reported a response rate of 31% in 41 women treated with mitomycin who had been previously treated with CMF [7]. DeLena et al. reported responses to mitomycin in five of 22 previously treated patients [3]. Four of these responders had prior treatment with CMF and vincristine plus doxorubicin. The optimal schedule for mitomycin administration has not been determined. The use of several daily doses in the initial studies of this compound by the Japanese revealed an objective response rate in 11 of 26 patients [5]. The use of a weekly schedule failed to ameliorate myelosuppression and no responses were seen in 12 breast cancer patients [11]. The use of large, 10–20 mg, doses of mitomycin given at 4–6 week intervals in women with far advanced breast cancer was studied by Wise et al., who noted a 26% response rate in 54 patients [16]. The median duration of response was 2.5 months, with a range of 1–8 months. Almost all patients had prior chemotherapy and the toxicity data were similar to those recorded in studies using the less convenient protracted low-dose schedule. The use of an intermittent dose schedule was selected for use in this study because of its convenience.

In this study mitomycin was added to the combination of vincristine and doxorubicin to determine whether this combination could produce a higher response rate and longer duration of response than vincristine and doxorubicin or doxorubicin used alone. This combination (VAM) was utilized in patients who had failed to respond to CMF chemotherapy given either as an adjuvant or for advanced disease.

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Materials and methods

Thirty-seven patients with recurrent or progressive breast carcinoma were entered into the trial between July, 1979 and February, 1981. All patients had a histologically confirmed diagnosis of breast carcinoma with recurrence or progression during prior chemotherapy. The patients had not been treated for at least 2 weeks prior to study. Written informed consent meeting all federal, state, and institutional requirements was obtained prior to placement on study. Patients who had been previously treated with vincristine, doxorubicin, or mitomycin; patients with brain metastases as the only evidence of metastatic disease; or patients with clinical signs of congestive heart failure were excluded. Patients received vincristine 1.5 mg/m^2 (maximum 2.0 mg) and doxorubicin 40 mg/m^2 on day 1 and day 22 of each 42-day cycle. On day 1 they also received mitomycin C 10 mg/m^2 and this was repeated on day 42. Doxorubicin was discontinued at a total dose of 450 mg/m^2. If a patient had received radiation therapy to the axial skeleton within the past 6 months, a 25% dose reduction was made on day 1 of the first course. Subsequent courses were increased to 100% of the calculated dosage if no myelosuppression occurred. Full doses of chemotherapy were given if the white blood cell count was greater than 4,000/μl and the platelet count was greater than 100,000/μl. Half-dosage was given with white blood cell counts between 3,000 and 4,000/μl and platelet counts greater than 100,000/μl. For blood counts below these levels the drugs were withheld and counts checked weekly. Vincristine was omitted for severe paresthesias or motor loss. Appropriate dose modifications were made for doxorubicin in patients with elevated liver function tests.

Pretreatment studies included history and physical examination, assessment of performance status, measurement of indicator lesions, CBC, platelet count, SMA, chest X-ray, and electrocardiogram. A skeletal survey was done to assess skeletal metastases and was used for follow-up evaluation if positive. In patients with a negative bone survey and a positive bone scan, the bone scan was used to evaluate skeletal disease. Liver scans were only done in patients with elevated alkaline phosphatase, and brain scan or CT scans were only done if clinically indicated. Blood counts were done prior to each treatment course, and assessment of response for soft tissue, palpable and chest metastases was done every 6 weeks. Appropriate skeletal X-rays, bone scans, and liver scans were repeated every 3 months if initially abnormal.

Assessment of response was standardized according to criteria outlined by the International Union Against Cancer [9]. A diminution in lesion size had to be present for at least 4 weeks to be considered a response. Duration of response was calculated from the first day of treatment to date of progression, or last date of follow-up. Survival was calculated from the date of initiation of therapy until death. The survivorship and duration of response distributions were estimated according to the method given by Kaplan and Meier [12]. Gehan's modification of the Wilcoxon test for censored data was used to test for differences among these time distributions [6].

Results

There were 37 patients entered on study. One patient withdrew due to severe nausea and vomiting after one course of therapy, leaving 36 patients evaluable. Pretreatment characteristics of the patients are noted in Table 1. All patients had previous chemotherapy with CMF, 15 (42%) having received this as adjuvant treatment. Hormonal therapy had also been administered to 19 of the patients.

Table 1. Patient characteristics and response

	Pretreatment no. (%)	CR + PR no. (%)	Stab no. (%)	Prog no. (%)
Evaluable patients	36 (100)	11 (31)	12 (33)	13 (36)
Age (median, range)	52 (26–72)	52 (32–72)	55 (38–70)	53 (26–69)
Age > 50	23 (64)	7 (30)	8 (35)	8 (35)
Performance 0–2	33 (92)	11 (33)	12 (36)	10 (30)
DFI < 2 years	22 (61)	7 (32)	5 (23)	10 (45)
Prior therapy				
Surgery	36 (100)	11 (31)	12 (33)	13 (36)
Radiation	23 (64)	5 (22)	7 (30)	11 (48)
Hormonal	19 (53)	7 (37)	6 (32)	6 (32)
Chemotherapy CMF-ADJ	15 (42)	8 (53)	3 (20)	4 (27)
CMF-ADV	21 (58)	3 (14)	9 (43)	9 (43)
OTHER + CMF	6 (17)	0	2 (33)	4 (67)
Estrogen receptors				
Positive	7 (19)	2 (29)	1 (14)	4 (57)
Negative	16 (44)	6 (38)	4 (25)	6 (38)
Unknown	13 (36)	3 (23)	7 (54)	3 (23)
Dominant site				
Soft tissue	1 (3)	0	0	1 (100)
Bone	10 (28)	4 (40)	3 (30)	3 (30)
Viscera	25 (69)	7 (28)	9 (36)	9 (36)
Number of sites				
1	14 (39)	4 (29)	5 (36)	5 (36)
2	10 (28)	4 (40)	2 (20)	4 (40)
≥ 3	12 (33)	3 (25)	5 (42)	4 (33)

Response to treatment is also noted in Table 1. Of 36 patients, 11 (31%) had a complete or partial response. The one patient with a complete response had had 2 months of CMF adjuvant therapy prior to documented progression in lymph nodes, bone, and liver. After seven courses of VAM therapy, physical examination and bone and liver scans were normal. The CR lasted 7 months until relapse was noted in subcutaneous tissue. Ten patients had a partial response. The median duration of complete and partial responses in the study was 5 months. One patient remains on study after 12 months of chemotherapy. Two patients who had partially responded to treatment were taken off protocol for unrelated reasons. Most patients relapsed at sites initially involved prior to being placed on study and two experienced relapse in the central nervous system.

Twelve patients had stable disease while on protocol. The median duration of response for these patients was 4.6 months, which is not significantly different from those obtaining CR or PR. No pretreatment characteristic is able to predict which patients might achieve response, except for prior chemotherapy. Of 15 patients receiving CMF as an adjuvant, eight (53%) responded, as opposed to three of 21 (14%) who received CMF

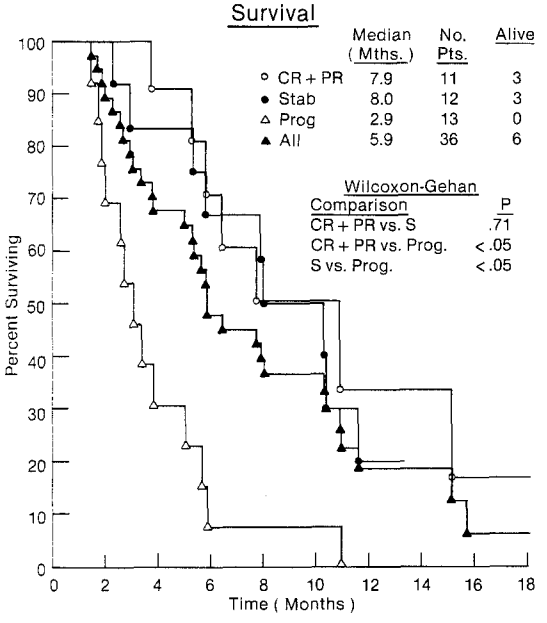

Fig. 1. Survival versus time (months)

Table 2. Toxicity: maximum per patient

	No. (%)
Total Patients	36 (100)
Hemoglobin < 9 g%	5 (14)
WBC (μl)	
≥ 4,000	13 (36)
2,000–3,999	18 (50)
1,000–1,999	4 (11)
< 1,000	1 (3)
Platelets (× 10^3/μl)	
≥ 100	23 (64)
50–99	7 (19)
24–49	6 (17)
< 20	0 (0)
Nausea/vomiting[a]	
Grade 0–1	25 (69)
Grade 2	5 (14)
Grade 3	6 (17)
Grade 4	0 (0)

[a] See ref. [14] for grading criteria

for advanced disease. Patients who had received CMF as an adjuvant and those who received CMF for advanced disease did not differ significantly in age, performance status, disease-free interval, dominant site of disease, number of sites of disease, or estrogen receptor status. In spite of this difference in response rate, the median survival for patients failing CMF as adjuvant therapy or for advanced disease was similar, at 5.7 and 6.9 months, respectively. This indicates that a higher response rate does not necessarily lead to improved survival.

Survival data are presented in Fig. 1. There is no significant difference in median survival between patients obtaining complete or partial response versus those with stable disease. There is a significant difference, however, between these two groups and patients with progression ($P < 0.05$). The maximum hematologic toxicity per patient is presented in Table 2. Myelosuppression was moderate except in one patient, who developed a white blood cell count of 200/μl and was hospitalized for fever and presumed sepsis. This patient recovered uneventfully. One patient developed severe motor weakness with foot drop, which was felt to be due to vincristine. One patient was hospitalized for thrombophlebitis. Nausea and vomiting were moderate and alopecia was seen in all patients. Cardiotoxicity was not observed in this study.

Discussion

Brambilla and colleagues reported five PRs in 23 patients treated with vincristine and doxorubicin after failure of CMF. The median duration of response was 4.5 months, similar to that observed in this study. Recently, Oster and colleagues presented their preliminary data concerning administration of vincristine, doxorubicin, and mitomycin to 15 women who had failed prior chemotherapy [15]. Of their 15 patients, 11 (73%) achieved CR or PR (3 + 8), with a median duration of 11 months. Eight of these responses were in soft tissue and no response was specified for patients with bone metastases. These authors utilized similar dosage and schedule for VAM. It is possible that their impressive preliminary findings were due to a different distribution of metastatic lesions in the patients they studied, and it will be important to note whether their results hold after additional patients are added. Another recent report indicates that mitomycin, when used as first-line chemotherapy with doxorubicin, may result in an improved response rate, with 10 of 35 patients achieving CR [4]. These preliminary data are encouraging and hopefully will be substantiated in larger numbers of patients.

The response rate and duration observed for the VAM combination utilized in this study was not superior to other second-line treatment programs utilizing single agents or potentially less toxic combinations [8]. Although mitomycin has been shown to be an effective single agent in patients with metastatic breast cancer it remains to be shown whether it will add to currently used combinations. Encouraging preliminary results utilizing mitomycin and doxorubicin as first-line treatment should be confirmed.

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