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Adriamycin, vinblastine and mitomycin C as second-line chemotherapy in advanced breast cancer

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Summary. Thirty-six evaluable patients with metastatic measurable breast carcinoma previously treated with CMF or CMFVP were given second-line chemotherapy with Adriamycin, vinblastine, and mitomycin C (AVM), as follows: Adriamycin 20 mg/m^2 and vinblastine 6 mg/m^2 by i. v. push on days 1, 8, and 15, and mitomycin C 10 mg/m^2 i. v. on day 1, every 6 weeks. Ten patients (28%) achieved partial remission (PR) lasting a median of 10 months, and eight patients (22%) experienced improvement of a lesser level than PR. An additional nine patients (25%) had disease stabilization; in the remaining nine patients (25%), persistent disease progression was observed. The median survival from the onset of AVM was 7 months for all patients; patients with PR survived a median of 13 months.

Myelotoxicity was substantial and frequently interfered with the optimal administration of AVM, especially in patients with skeletal metastases; four patients were hospitalized with leukopenia and fever; all recovered promptly; one death was probably related to thrombocytopenia and CNS bleeding.

Our results with AVM are similar to the average response rate published in the literature with the use of Adriamycin as a single agent in previously treated patients with advanced breast cancer.

Introduction

Metastatic breast cancer, although a chemosensitive tumor, remains an incurable disease. The majority of the treated patients will respond to first-line chemotherapy and enjoy higher quality of life and longer survival than nonresponders [1, 18]. Most patients, however, will eventually require second-line chemotherapy after failing first-line treatment. There is no established, conventional second-line chemotherapy program for breast cancer patients. For patients failing widely used regimens, such as CMF or CMFVP [1], second-line schemes are usually Adriamycin-based, since Adriamycin is one of the most active single agents in breast cancer [36] and has resulted in response rates ranging from 20% to 38% when given as a single agent in previously treated patients [11, 17].

Other drugs frequently used in patients failing CMF, with or without vincristine and prednisone, are vinblastine and mitomycin C. The activity of both as single agents in breast cancer has been well documented. Mitomycin C for instance, resulted in an 18% response rate when given to 90 patients in a Southwest Oncology Group (SWOG) study [4]. Response rates to vinblastine as a single agent have ranged from an average of 20% to one of 40%, depending on whether the drug is given by i. v. push or by continuous infusion [35]. Furthermore, mitomycin C and vinblastine are thought to be synergistic in vitro [28]. In the clinical setting, the combination of mitomycin C and adriamycin has been effective in stiuations usually resistant to a variety of other regimens [34]. Despite the effectiveness of these three drugs, they have seldom been given together in combination in breast cancer.

We report here our experience with the administration of Adriamycin, vinblastine, and mitomycin C (AVM) given in an intensive schedule to 39 patients with metasatic breast cancer previously treated with CMF or CMFVP.

Materials and methods

Thirty-nine patients suffering from measurable metastatic breast cancer who had failed prior systemic chemotherapy with the CMF (cyclophosphamide, methotrexate, 5-fluorouracil) combination, with or without the addition of vincristine and prednisone (CMFVP), were entered into this study between August, 1982, and July, 1984. In eight patients, chemotherapy had been given in the adjuvant setting only, with a median interval of 9 months (range 7–18) from the last course of adjuvant chemotherapy to the onset of AVM. An additional seven patients, who presented with advanced locoregional disease, stage III, were given CMF as part of a multimodality program which also included X-ray therapy to the affected breast and regional lymph node-bearing areas; in this group of patients the median interval from prior chemotherapy to AVM was 4 months (1–17); eleven patients who had received adjuvant chemotherapy with CMF were retreated with CMFVP at their first relapse; the remaining thirteen patients had known metastatic disease when treated with first-line chemotherapy; the median interval from the last course of previous chemotherapy given for measurable metastatic diesease to the onset of AVM was 1 month (1–24) (Table 1). All patients had discontinued chemotherapy at least 4 weeks before entry into the study. Two of the patients had been treated with Adriamycin in addition to either CMF or

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Table 1. Pretreatment characteristics

No. of patients	39
No. evaluable for toxicity	39
No. evaluable for response	36
Median age at diagnosis, years (range)	44 (27–72)
Median age at AVM, years (range)	46 (29–73)
Menopausal status at diagnosis	
Pre	21
Post	17
Unknown	1
Median disease-free interval, months (range)	12 (0–288)
Median Karnofsky performance status at AVM, %, (range)	80 (40–100)
Prior treatment	
Radiation therapy	
Chest wall and regional lymph nodes	24
skeletal metastases	10
Hormone therapy	
Tamoxifen	18
Aminoglutethimide	3
Oophorectomy	2
Chemotherapy	
Adjuvant only (stages II & III)	15
Adjuvant + retreatment at first relapse	11
For active disease only	13
Metastatic sites at AVM	
Skeleton	21
Lung/pleura	15
Liver	14
Skin, soft tissue	13
Regional lymph nodes	7
Breast	5
Bone marrow	3
Pericardium	2
No. of metastatic sites	
1	13
2	12
3	12
4	2

CMFVP. One had received vincristine and Adriamycin to a total dose of 170 mg; a second patient had been given six 3-weekly courses of Adriamycin as a single agent, to a total dose of 300 mg. None of the patients had been exposed to either vinblastine or mitomycin C. All patients were evaluable for toxicity, and thirty-six patients were evaluable for response, including both patients previously exposed to Adriamycin. Three patients were not evaluable for response; all three had received less than one full course of chemotherapy: one was given hormonal treatment at another institution, a second patient refused further treatment, and another was lost to follow up.

Patient evaluation prior to AVM chemotherapy included physical examination with careful tumor measurements; complete hemogram and blood biochemistry; electrocardiogram; chest X-ray, liver and bone scans, and CEA plasma levels. Skeletal survey and bone marrow biopsy were obtained when clinically indicated. Patients had to have adequate blood counts, defined as WBC >3500 and platelets >100000 per mm^3, except in cases with documented bone marrow tumor involvement. None of the patients had evidence of heart disease or renal failure at the onset of AVM chemotherapy.

Complete blood counts were available prior to each dose of chemotherapy. Tumor measurements and blood biochemistry were repeated monthly. Chest X-ray, and liver and bone scans were obtained every 3 months, or earlier when necessary. Baseline left ventricular ejection fraction (LVEF) was determined in most patients, and in all patients after a cumulative dose of Adriamycin of 450 mg/m^2 had been reached. Performance status was determined according to the Karnofsky scale [19]. Response to chemotherapy was defined using established criteria [16]. Duration of response and survival was calculated from the onset of AVM chemotherapy. Comparison of the significance of findings was done by the Chi-square and Breslow tests. Data were last analyzed in February 1985.

The AVM regimen consisted in the administration of Adriamycin 20 mg/m^2 and vinblastine 6 mg/m^2 by i.v. push on days 1, 8, and 15 of the course, and mitomycin C 10 mg/m^2 i.v. on day 1 of each cycle, which was repeated every 6 weeks. Adriamycin was delivered weekly following reports suggesting a decreased risk of cardiotoxicity with this schedule [30, 32]; this drug was discontinued after a total dose of 450 mg/m^2 was reached; chemotherapy then continued with vinblastine and mitomycin C only, with unchanged doses and schedule; the doses of all three drugs were adjusted according to the degree of myelosuppression. Overall, a total of 163 cycles of AVM had been delivered at the time this analysis was undertaken, with a median of 3 and a mean of 4.2 courses of AVM per patient (range, 1–14).

Pretreatment patient characteristics are shown in Table 1. Patients had a median age of 46 years at the onset of AVM; most were ambulatory, with a median performance status of 80% (Karnofsky scale); in addition to previous chemotherapy, 24 patients had also received prior radiation therapy to the affected breast (or chest wall, postmastectomy) and regional lymph node-bearing areas, and 10 patients had been irradiated for palliation to painful skeletal metastases; 18 of the 39 patients had been given tamoxifen and 3 of these subsequently received aminoglutethimide as well. Hormone therapy had been discontinued in these patients at least 4 weeks before AVM administration. The most frequent metastatic sites were the skeleton, the lungs, the liver, and soft tissue. Two patients had four metastatic sites; patients with one, two, or three sites were similarly distributed (Table 1).

Results

There were no complete remissions. Of 36 evaluable patients, 10 (28%) achieved a partial remission (PR) lasting a median of 10 months (range 3–18 months); 8 patients (22%) experienced improvement of a lesser degree than PR for a median of 3.5 months (2–7). In 9 further patients (25%) AVM resulted in stabilization of disease for a median of 4 months ($2-10^+$); in 9 patients (25%) the disease continued to progress during AVM chemotherapy.

Partial responses occurred in visceral and nonvisceral metastatic sites including 5 of 14 patients, with liver involvement and 6 of 21 with skeletal metastases; only 2 of 15 patients with pleural and/or lung involvement achieved

Table 2. Given dose as a percentage of the originally planned dose by cycles of AVM

Cycle no.	1	2	3	4	5	6 or more	Overall
No of pts treated	39	31	26	16	9	8	39
Drug							
Adriamicin	74%	76%	78%	73%	69%	52%	73%
Vinblastine	73%	74%	75%	70%	65%	55%	71%
Mitomycin C	95%	91%	89%	90%	90%	80%	92%

Table 3. Toxicity to AVM

	No. of pts	(%)
Nausea and vomiting	39	(100)
Alopecia (total or partial)	39	(100)
Severe stomatitis	1	(3)
Leukopenia (median $1.4 \times 10^3/mm^3$, range 0.3–3.0)		
$< 2.0 \times 10^3$	28	(72)
$< 1.0 \times 10^3$	11	(28)
Leukopenia and fever	4	(10)
Thrombocytopenia (median $133 \times 10^3/mm^3$, range 29–368)		
$< 100 \times 10^3$	14	(36)
$< 50 \times 10^3$	3	(8)
Bleeding	1	(3)
Cardiotoxicity	1	(3)
Chronic renal failure	1	(3)

PR with AVM. Responders had a median of two metastatic sites, as against a median of three sites in progressors.

The median survival from the onset of AVM was 7 months ($1-26^+$) for all patients evaluable for response and 13 months ($6-26^+$) for partial responders.

Response to AVM did not correlate with the patients' age at the onset of this treatment; however, patients who were premenopausal at the diagnosis of breast cancer had a higher response rate to AVM (37%) than their postmenopausal counterparts (18%). Also, patients with a performance status of 80% or higher had a PR rate of 32%, as opposed to 21% in patients who started AVM therapy with a performance status below 80%. These differences are not statistically significant. Neither the percentage of doses of AVM actually given nor the degree of myelosuppression predicted for response to chemotherapy. In fact, the median nadir leukocyte count of responders was $1250/mm^3$, not significantly different than the median nadir WBC count of $1400/mm^3$ for the entire group of treated patients.

Response to first-line chemotherapy also did not allow discrimination between responders and nonresponders to AVM. Of the 10 responders to AVM, 7 had measurable metastatic disease during CMF or CMFVP treatment, 2 had a PR to first-line treatment, 3 had stabilization of disease, and 2 had had disease progression and never responded befor going on to respond to AVM.

For those 15 patients in whom first-line chemotherapy had been given in the absence of clinically evident metastases (stages II and III disease), the rate of PR with AVM given upon relapse was similar to that achieved by patients who had systemic measurable disease at presentation and were first given CMF-CMFVP and subsequently AVM (27% vs 28%).

Substantial myelosuppression occurred frequently during treatment with AVM. For this reason, in the majority of patients the third weekly dose of Adriamycin and vinblastine was either delayed by 1 week or cancelled altogether at some point. In fact, only 8 of the 39 patients (21%) received all three doses per course in all courses given, and only 42% of all cycles of AVM consisted of three doses as originally planned, including 52% of the cycles given to patients without bone involvement, as against 37% of the courses given to patients with skeletal metastases.

The given dose as a percentage of the planned dose for all courses of AVM was 73% for Adriamycin, 71% for vinblastine, and 92% for mitomycin C, reflecting the difficulty frequently encountered in delivering the third dose of Adriamycin and vinblastine because of myelosuppression. The percentages of the planned doses of AVM given are shown course by course in Table 2. A marked decrease in the given doses was observed only after six or more courses of chemotherapy had been administered. No significant difference in overall given doses was observed between patients with or without bone involvement (Adriamycin 71% vs 75%; vinblastine 70% vs 71%; and mitomycin C 91% vs 93%). In spite of substantial myelosuppression, the interval between courses was not prolonged and remained at 42 days as originally planned, even in patients given five or more cycles of AVM chemotherapy and regardless of the presence of bone metastases.

Toxicity

Toxicity to AVM is summarized in Table 3. Nausea and vomiting were universal. One patient suffered from severe stomatitis. Myelosuppression, mainly leukopenia, was the most important toxicity observed with this regimen. The median nadir leukocyte count was $1400/mm^3$ (300–3000). Of the 39 patients 28 (72%) experienced leukopenia with $< 2000/mm^3$, and 11 patients (28%) had leukopenia with $< 1000/mm^3$ at least once; four patients had a total of five hospitalizations because of fever while leukopenic. In three episodes no source of infection was identified; two patients had urosepsis attributable variously to *Klebsiella pneumoniae* and *Escherichia coli*, respectively. All four patients recovered promptly with i. v. antibiotics.

The degree of leukopenia was only moderately influenced by the number of cycles of AVM. Thus, the median nadir WBC count during the first course of AVM was $3100/mm^3$ (600–7700) as against a median of $1900/mm^3$ (300–4700) during the last course of chemotherapy in patients given more than one cycle of AVM. The median nadir WBC count usually occurred between days 13 and 15 of the cycle (range, day 4–24). Recovery of the WBC count was usually prompt.

Thrombocytopenia was of lesser significance. The median nadir platelet count recorded was $133000/mm^3$

(29000–368000). Fourteen patients (36%) experienced thrombocytopenia of $<100000/mm^3$; there was one episode of severe GI bleeding in a patient with a nadir count of $29000/mm^3$. This patient died on day 17 of the first course of chemotherapy, which had been given on days 1 and 8 only, presumably from CNS bleeding; an autopsy was not performed, but bone marrow involvement had been documented in this patient, who started AVM with a platelet count of $74000/mm^3$. The median nadir platelet count was also observed on day 14 of the cycle (range, day 7–45), again with prompt recovery to normal values. Nine patients (24%) required blood transfusions for anemia during AVM medication.

Other complications resulting from the administration of AVM included, in one patient, a significant drop in LVEF to 47%, without overt congestive heart failure, after a cumulative Adriamycin dose of 450 mg/m^2; in addition, this patient, who achieved PR with AVM, also developed chronic renal failure following 11 courses of AVM, with a fall in creatinine clearance to 25 ml/min, when she had been given a total dose of 166 mg mitomycin C. A second responding patient developed, and eventually died of, microangiopathic hemolytic anemia (MAHA) after a total of nine cycles of AVM and a cumulative dose of mitomycin C of 118 mg; at the time of diagnosis of MAHA the bone marrow was heavily infiltrated by tumor cells. Neither pulmonary nor neurological toxicity were observed in our patient population.

Discussion

AVM as given here had limited effectiveness as second-line chemotherapy in patients with advanced breast cancer, although our protocol called for a fairly intensive schedule, with Adriamycin and vinblastine administered at weekly doses similar to those used when either is given as a single agent [12, 30, 32]. Indeed, myelotoxicity was significant, with nadir leukocyte counts below $1000/mm^3$ observed in 28% of the treated patients and with 10% of the patients hospitalized for leukopenia and fever. In addition, there was one death, probably related to profound thrombocytopenia. Furthermore, myelosuppression frequently precluded the fulfillment of the original schedule of AVM, even in the absence of skeletal metastases. Neither the dose levels of AVM nor the degree of myelosuppression allowed discrimination between responders and nonresponders.

Other commonly observed toxicities to AVM, in addition to myelosuppression, included nausea, vomiting, and alopecia. One patient experienced irreversible renal damage following a total mitomycin C dose of 166 mg. A second patient died with MAHA; she had received a cu-

Table 4. Representative series of salvage chemotherapy programs in breast cancer with A.V.M. (Adriamycin, vinblastine, and mitomycin C) as single agents or in combinations

Agent/combination	Authors	Ref.	No. of evaluable pts	Response rate (CR + PR)
Adriamycin	Gottlieb et al.	[11]	40	38%
	Manni et al.	[22]	59	34%
	Tormey	[29]	253	28%
	Creech et al.	[3]	60	27%
	Cowan et al.	[2]	35	26%
	Fredericksen et al.	[8]	30	23%
	Hoogstraten et al.	[17]	49	20%
Vinblastine	Yap et al.	[35]	30	40%
Mitomycin C	Wise et al.	[33]	54	26%
	DeLena et al.	[5]	23	23%
	Creech et al.	[4]	90	18%
	Pasterz et al.	[25]	43	12%
VAM	Oster and Park	[24]	15	73%
ADM	Pinnamaneni et al.	[27]	26	54%
	Distefano et al.	[7]	26	53%
VATH (5-day)	Perloff et al.	[26]	19	52%
VATH (1-day)	Hart et al.	[15]	29	45%
FOAM	Friedman et al.	[9]	82	35%
AM	Morgan	[23]	19	40%
	Harris et al.	[14]	24	25%
MMC-VLB	Konits et al.	[20]	30	40%
	Garewal et al.	[10]	22	32%
	Denefrio et al.	[6]	14	7%
AVM	Luikart et al.	[21]	27	33%
	Present trial	–	36	28%

Abbreviations: VAM, vincristine, Adriamycin, mitomycin C; ADM, Adriamycin, dibromodulcitol, mitomycin C; VATH, vinblastine, Adriamycin, thioTEPA, halotestin; FOAM, 5-fluorouracil, vincristine, Adriamycin, mitomycin C; AM, Adriamycin, mitomycin C; MMC-VLB, Mitomycin C, vinblastine; AVM, Adriamycin, vinblastine, mitomycin C

mulative mitomycin C dose of 118 mg and at diagnosis of MAHA she had evidence of extensive bone marrow replacement by tumor. Reviews of these complications have recently been published [13, 31].

The 28% PR rate obtained with AVM was disappointing. Several published Adriamycin-based 'salvage' chemotherapy programs for patients with metastatic breast cancer previously treated with CMF or CMFVP have shown higher objective remission rates. Table 4 summarizes the effectiveness of Adriamycin, vinblastine, and mitomycin C as single agents in previously treated patients with breast cancer, compared with a number of combination chemotherapy schemes including, among other drugs, at least two of the three agents we have employed in this study. It appears from this review of some representative published studies that Adriamycin-based regimens function somewhat better than either single agents or combinations lacking Adriamycin as salvage schemes in previously treated patients with breast cancer. Thus, while the mean response rate to Adriamycin as a single agent in these studies [2, 3, 8, 11, 17, 22, 29] is 28%, and that to mitomycin C is 20% ([4, 5, 25, 33], the mean response rate for those Adriamycin-containing combinations shown in Table 4, excluding our series [7, 9, 14, 15, 21, 23, 24, 26, 27], is higher at 45%. Results with the combination of vinblastine and mitomycin C [6, 10, 20] do not seem to differ from those obtained with Adriamycin as a single agent.

These results are, of course, from different institutions, utilizing similar but certainly not the same chemotherapy combinations for the treatment of a disease that is typically heterogeneous, such as breast cancer, and therefore any comparison must be viewed with caution. A number of factors, including the distribution of prognostic characteristics among patients in the different studies, must be taken into account. This is illustrated by contrasting the results of Oster and Park [24], who obtained a 73% response rate with vincristine, Adriamycin, and mitomycin C, and those of Denefrio et al. [6], who utilized mitomycin C and vinblastine and obtained an objective response of only 7%; 8 of 11 responses reported by Oster et al. occurred in patients with soft tissue metastases; Denefrio et al. observed only 1 response among 14 patients, 53% of whom had predominantly visceral disease and about as many (47%) had three or more metastatic sites.

Despite the profusion of second-line chemotherapy regimens tried in patients with advanced breast cancer, published experience with the combination of Adriamycin, vinblastine and mitomycin C is sparse. Recently, Luikart et al. at the Yale Comprehensive Cancer Center reported their results with AVM in 27 evaluable patients with metastatic breast cancer, all of whom had been treated with methotrexate and 5FU, plus cyclophosphamide (23 patients) or Adriamycin (3 patients) [21]. There were 3 complete remissions and 6 PRs, for an overall objective response rate of 33%, and a median time to progression of close to 4 months, results which are in agreement with ours. The AVM regimen in their study, however, differed from ours in the doses and schedule of Adriamycin and vinblastine, which were less intensive: Adriamycin 30 mg/m^2 and vinblastine 6 mg/m^2, both on days 1 and 28 only, while mitomycin C 10 mg/m^2 was given on day 1, and cycles were repeated at longer intervals, i.e., once every 8 weeks. Their regimen resulted in significant myelosuppression as well; while nadir counts were not reported, 22% of the patients experienced leukopenia of <1000 and 33% had thrombocytopenia of $<100000/mm^3$; 37% of the patients required dose reduction, but in agreement with our findings, decreased doses did not result in lower response rates in these patients. The authors concluded that AVM is probably not superior to Adriamycin as a single agent as second-line treatment in metastatic breast cancer.

Since in our study too AVM does not appear to represent an improvement over single agent chemotherapy as second-line treatment in advanced breast cancer, we are now planning to give these three drugs, Adriamycin, vinblastine, and mitomycin C sequentially as single agents. Our aim would be twofold: to explore the possibility of reinducing response and to prolong survival in breast cancer patients failing first-line chemotherapy with either CMF or CMFVP; and at the same time, to attempt to ameliorate the considerable toxicity observed when all three drugs are given in combination.

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