

A Randomized Trial of Two Dosage Schedules of Mitomycin C in Advanced Breast Carcinoma

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For mitomycin C (MMC), an effective agent in the treatment of metastatic breast cancer, the optimal dosing strategy in responding patients must be defined because of the dose-limiting, long-term hematologic toxic effects. Sixty-seven patients received treatment for metastatic breast cancer (MMC 20 mg/m², intravenously) and then were selected randomly to receive either "standard doses" (SD) (20 mg/m², intravenously) or "low doses" (LD) (5 mg/m², intravenously) of MMC every 6 weeks. The primary objective was to show that the LD regimen would result in fewer toxic effects and at least equal disease control. Response rates in the two arms were similar: there were no complete responses and five partial responses (15%) in the SD group and two complete responses and six partial responses (24%) in the LD group ($P = 0.332$). In the SD and LD groups, median times to progression (11 versus 12 weeks, respectively), response duration (10 versus 6½ weeks, respectively), and survival (26 versus 26 weeks, respectively) were similar. The hematologic toxicity was significantly less in the LD group. Nine patients in the LD group were treated with SD at disease progression, and one complete response was observed. It is concluded that, in this group of patients, administration of MMC in LD, compared with SD, resulted in fewer hematologic toxic effects and similar disease control. *Cancer* 1992; 69: 476-481.

Mitomycin C (MMC) (Mutamycin, Bristol Laboratories, Syracuse, NY) is an effective anticancer agent first isolated in Japan in 1958¹ and released for commercial use

in the United States in 1974. Crooke and Bradner² reviewed the literature on this agent published until 1976. An update by Doll *et al.*³ summarized its efficacy in various gastrointestinal, pulmonary, genitourinary, squamous cell, and breast cancers. In their article, they reviewed its mechanism as an alkylating agent, teratogenic and carcinogenic properties, and pharmacokinetics.³

Beginning in 1958, most clinical trials used a daily dosage schedule of 1 to 7 mg for 4 to 85 days.⁴⁻⁶ This corresponded to daily dosages of 0.625 to 4.375 mg/m²/d and total doses of 2.5 to 370 mg/m². Because daily administration schedules were associated with severe myelosuppression, intermittent schedules were developed and came to be the standard method of therapy.⁷⁻¹⁰ The initial belief, that the objective response rate correlated with total dose,⁴ was replaced by the experience that responders necessarily received more treatment. The median dose level in responders, at the time response was achieved, was lower than the total cumulative dose for nonresponders, suggesting that the larger cumulative dose for responders was the result and not the cause of objective response. The "standard" dosage of MMC used as a single agent is now 15 to 20 mg/m² every 6 to 8 weeks.

Therefore, although toxicity is clearly dose related, response is not, and the long-term effect of dosage on continued response has not been defined. Our clinical observation suggested that response sometimes is lost in some patients because of the inability to deliver timely, effective doses.

Single-agent data for MMC in breast cancer have been reported by Godfrey,¹¹ Creech *et al.*,¹² Hum *et al.*,¹³ and Moore *et al.*,¹⁴ and the single-agent response rates in previously treated patients have been consistently between 15% and 25%.

Because of these considerations, we designed a randomized trial to investigate two different dosage sched-

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ules in the chronic therapy of patients with metastatic breast cancer. The question we asked was whether a lower-dosage maintenance schedule (with presumed decreased clinical toxic effects) would result in clinical efficacy similar to that of a more conventional dosage regimen.

Materials and Methods

Between March 1987 and October 1988, 67 patients with metastatic breast cancer were assigned randomly to one of two arms of treatment with MMC. Eligibility criteria included the following: (1) histologic proof of metastatic breast cancer; (2) three or fewer prior chemotherapy regimens; (3) no previous exposure to mitomycin or nitrosoureas; (4) life expectancy of at least 12 weeks; (5) Zubrod 2 or lower performance status; (6) signed informed consent; (7) measurable or assessable disease; (8) age of at least 18 years; (9) recovery from previous chemotherapy, radiation therapy, or immunotherapy; (10) adequate bone marrow (absolute granulocytes at least 1,800 and platelets at least 100,000), hepatic (bilirubin level < 1.6 mg/dl), and renal (serum creatinine level < 1.5 mg/dl) function; (11) controlled brain metastases, if they were present; and (12) adequate cardiac function (ejection fraction > 50%).

A complete response was defined as the disappearance of all evidence of tumor for at least 4 weeks. Bone lesions were to have improved, as shown by scans, or to have completely reossified, as shown on routine radiographs. Patients were to be free of all symptoms of cancer. A partial response was defined as a 50% or greater decrease in the sum of the products of the diameters of all measured lesions persisting for at least one cycle of therapy or 4 weeks. Nonmeasurable lesions must have decreased by at least 50%. No lesion could increase in size, and no new lesions could appear. A minor response was defined as a measurable decrease in lesions that was either too small or too brief to qualify as a partial remission. For purposes of analysis, minor responses were counted as failures, although they may have indicated biologic activity. Progressive disease was defined as any increase greater than 25% in the sum of the products of diameters of any measurable lesion or in estimated size of nonmeasurable lesions, or as the appearance of any new lesions. Failure was indicated by no change, progressive disease, or a minor response. Response duration was measured from the time of response to evidence of progressive disease; time to progression was measured from the start of therapy until evidence of progressive disease; and survival was calculated from the start of therapy until the patient died or was lost to follow-up.

Survival comparisons were performed with the Kaplan-Meier method,¹⁵ and responses were compared by Fisher's exact test.¹⁶ The calculation was that 42 patients per arm would be required to detect a 50% decrease in Grade 3 or 4 thrombocytopenia, or a ratio of 2 in median survival between the two arms (one-sided, $P = 0.05$, with a power of 80%). Because of the low response rate and response duration, the study was terminated before the projected accrual was achieved.

All patients received the same initial dose of 20 mg/m² of MMC as an intravenous injection on day 1. In patients who had received radiation therapy to more than four ports or at least 25% of functional bone marrow, treatment was initiated at the lower dose of 15 mg/m². At registration, patients were assigned randomly to receive maintenance dose levels of either standard-dose (SD) or low-dose (LD) mitomycin therapy. The dosage levels are outlined below in milligrams per square meter:

Treatment 1 (SD)

Level	-3	-2	-1	0
	5	10	15	20

Treatment 2 (LD)

Level	-3	-2	-1	0
	1.5	2.5	3.8	5

All maintenance doses were to be given every 6 weeks, or on recovery from the previous course.

Subsequent dosage modifications were performed to achieve nadir granulocyte counts of 500, platelet counts of 75,000, and Grade 0 to 2 nonhematologic toxic effects.

Therapy was planned for at least two courses in the absence of rapidly progressive disease and for at least three courses in patients who exhibited stable disease in the absence of Grade 3 or 4 toxic effects.

Pretreatment evaluation included a history and physical examination, complete blood count, urinalysis, chest roentgenogram, electrolyte levels, chemical survey, coagulation profile, and appropriate tests to evaluate the extent of disease. Tumor measurements were repeated before each subsequent course; more elaborate studies were performed every two courses.

Patients were removed from the study for the following reasons: progressive disease after at least two courses of therapy; the development of unpredictable, irreversible, or Grade 4 toxic effects; or the refusal of the patient to continue in the study.

Characteristics of the patient population are detailed in Table 1. As shown, randomization resulted in

Table 1. Population Characteristics (n = 67)

Characteristic	Arm 1 (standard) (n = 34)	Arm 2 (low dose) (n = 33)
Median age in yr (range)	51 (28-67)	51 (25-71)
Performance status (Karnofsky)		
0	8 (24%)	9 (27%)
1	16 (49%)	14 (42%)
2	9 (27%)	10 (30%)
Female/male	32/2	33
Prior therapy		
Chemotherapy	34	33
Hormones	20 (59%)	17 (52%)
Immunology	4 (12%)	1 (3%)
Radiation therapy	22 (65%)	23 (70%)
No. of prior regimens		
1	12 (35%)	13 (39%)
2	11 (32%)	12 (36%)
3	10 (29%)	6 (18%)
> 3	1 (3%)	2 (6%)
No. of prior agents		
3	6 (18%)	7 (21%)
> 3	28 (82%)	26 (79%)
No. of sites of disease		
1	8 (24%)	9 (27%)
2	8 (24%)	11 (33%)
3	11 (32%)	3 (9%)
> 3	7 (21%)	10 (30%)
Dominant site		
Visceral	25 (74%)	24 (73%)
Bone	5 (14%)	6 (18%)
Soft tissue	5 (12%)	3 (9%)
Menopausal status		
Pre	10 (29%)	10 (30%)
Post	22 (65%)	23 (70%)
N/A	2 (6%)	0
ER status		
+	17 (50%)	11 (33%)
-	14 (42%)	17 (52%)
Unknown	3 (8%)	5 (15%)

ER: estrogen receptor; NA: not applicable (males).

the comparability of patients in the SD and LD arms with regard to age (median, 51 years in each), performance status, type of previous therapies, number of previous regimens (mean, 2 versus 1.9), number of previous agents, sites of disease, dominant site of disease, menopausal status, and estrogen receptor status (Table 1).

Results

Response Data

The response data for patients in the two treatment arms are shown in Table 2. All patients received exactly

one induction course of 20 mg/m² MMC, except for two patients in the SD group and three in the LD arm in whom treatment was initiated with 15 mg/m². Overall response rates in the two treatment arms were not significantly different: 5 of 34 (15%) correspond with 8 of 33 (24%) ($P = 0.332$). All but one was seen after the first course of treatment. A significantly higher number of patients in treatment arm 1 displayed progressive disease after one course of therapy ($P = 0.038$), which is certainly a result of undefined patient characteristics, because the induction therapies were identical.

Responses in the dominant sites of disease were as follows: in the SD group, five partial remissions occurred in soft tissue (two patients), lung (two patients), and liver (one patient); in the LD group, two complete responses occurred in soft tissue, whereas the six partial remissions were seen in lung (two patients) and liver (four patients). The overall response rate of 13 of 67 (19%) is comparable to that of previous reports.

The 67 patients received a total of 120 courses of mitomycin (mean, 1.8 courses per patient). The distribution of courses did not vary between the treatment arms, other than that three patients were able to receive four courses of therapy in treatment arm 2. The median number of courses received was not significantly different between the two treatment arms (1.7 versus 1.9), nor was the number received after the induction course (1.3 in both). No one received more than four courses of MMC, because of progressive disease. Despite our intentions for the protocol, nearly half (29 of 67) of the patients received only one course of therapy. In all but one case (the patient refused to continue), this resulted from progressive disease.

Toxicity

Table 3 summarizes the hematologic toxicity. The data are presented for all patients, according to the treatment arm they received, and also for patients who received more than the first course (which was identical in the two arms). As is easily seen, patients in treatment arm 2, the LD group, had significantly less leukopenia, granulocytopenia, and thrombocytopenia. The difference in

Table 2. Response Data

	Arm 1 (n = 34)	Arm 2 (n = 33)	
Complete response	0	2 (6%)	$P = 0.332$
Partial response	5 (15%)	6 (18%)	
Minor response	1 (3%)	2 (5%)	
Stable disease	4 (12%)	8 (24%)	$P = 0.038$
Progression	24 (71%)	15 (26%)	

Table 3. Hematologic Toxicity

	All patients			Patients receiving more than first course		
	Arm 1 (standard; 56 courses)	Arm 2 (low dose; 64 courses)		Arm 1 (standard; 22 courses)	Arm 2 (low dose; 31 courses)	
Leukocyte count						
Median nadir	2.5	3.5		2.8	4.9	
Range	0.6-7.0	1.1-9.6	$P = 0.008$	0.7-4.8	2.5-9.6	$P = 0.034$
% Grade 3 or 4	30	12		14	0	
Granulocyte count						
Median nadir	1.5	2.3		1.7	2.6	
Range	0.3-4.9	0.3-7.7	$P = 0.004$	0.3-3.2	1.4-7.5	$P = 0.005$
% Grade 3 or 4	32	12		23	0	
Platelet count						
Median nadir	74	122		51	152	
Range	10-174	5-429	$P = 0.031$	10-174	60-289	$P = 0.023$
% Grade 3 or 4	30	14		20	0	
Anemia						
% Grade 3 or 4	13	6	$P = 0.238$	27	3	$P = 0.108$

anemia is significant only in patients receiving more than one course. No Grade 3 or 4 leukopenia, granulocytopenia, or thrombocytopenia was seen in the LD group, which confirms the known dose effect of MMC on hematologic toxicity.

Data on nonhematologic toxicity are presented in Table 4. Nausea and vomiting, stomatitis, malaise, and diarrhea were not decreased significantly by the administration of lower doses of MMC. Fewer infections were seen at the lower doses, consistent with the lower degree of granulocytopenia. Surprisingly, the incidence of

hemorrhage was similar, although the numbers are small. Less anorexia, malaise, and hemorrhage were observed at lower doses when only those patients who received more than one course were considered. Pulmonary toxic effects, as manifested by diffuse interstitial infiltrates not attributable to congestive heart failure or tumor, were seen in only two patients receiving SD. The hemolytic-uremic syndrome was manifested by one patient in each group. We could not draw significant conclusions regarding the two latter complications because too few patients received sufficient long-term therapy.

Table 4. Nonhematologic Toxicity (n = 67)

Toxic effects	Arm 1 (standard) (n = 34)	Arm 2 (low) (n = 33)	
Nausea/vomiting			
Grade 1 or 2	15 (44%)	18 (55%)	NS
Grade 3 or 4	3 (9%)	0	
Stomatitis			
Grade 1 or 2	7 (21%)	7 (21%)	NS
Anorexia	10 (29%)	4 (12%)	NS
Malaise			
Grade 1 or 2	12 (35%)	6 (18%)	NS
Grade 3	2 (6%)	2 (6%)	
Infection	8 (24%)	3 (9%)	NS
Diarrhea			
Grade 1 or 2	8 (24%)	8 (24%)	NS
Hemorrhage	3 (9%)	2 (6%)	NS
Pulmonary	2 (6%)	0	NS
Hemolytic-uremic	1 (3%)	1 (3%)	NS

NS: not significant.

Time to Progression, Response Duration, and Survival Data

Table 5 shows the data regarding time to disease progression, response duration, and survival of patients in the two treatment arms. Again, the two groups—specifically patients who received more than one course of therapy—were compared. There were no significant differences between the groups in regard to median time to progression (11 versus 12 weeks), response duration (10 versus 6½ weeks), or survival (26 versus 26 weeks). The administration of lower doses of MMC neither allowed more therapy to be administered nor had a detrimental effect on survival.

Crossover of Patients With LD to Subsequent SD

Table 6 summarizes data for nine patients who initially were selected randomly to receive the LD regimen and then, on progression of their disease, were reinduced

Table 5. Time to Progression, Duration of Response, and Survival

	All patients			Patients receiving more than first course		
	Arm 1 (standard) (n = 34)	Arm 2 (low dose) (n = 33)		Arm 1	Arm 2	
Median time to progression	11 wk	12 wk	NS	14 wk	13 wk	NS
Response duration	10 wk (n = 6)	6.5 wk (n = 10)	NS	10.5 wk	6 wk	NS
Survival						
Median	26 wk	26 wk	NS	30 wk	32 wk	NS
Range	5-86 wk	6-103 wk				

NS: not significant.

with the SD of MMC. As indicated, one of the nine had a complete response of more than 21 months duration and another achieved a partial remission but died of pulmonary toxicity 30 months later. Thus, there was some evidence of retention of a dose-response effect in patients in whom disease progressed on lower doses of mitomycin.

Discussion

The population group for this trial consisted of patients, mostly women, with metastatic breast cancer who had received a mean of two prior chemotherapeutic regimens. All were either estrogen receptor negative or had unsuccessful hormonal therapy. Seventy-four percent of the patients in each treatment arm had visceral involvement as the dominant site of disease (mostly liver and parenchymal lung). The population was approximately two-thirds postmenopausal.

The overall response rate in these patients who received identical initial doses of MMC at 20 mg/m² was 19%, which compares favorably with previous reports. As usual, most of the responses were partial remissions, with only two complete remissions occurring. In 39 of the 67 patients, progressive disease was found after the

first course of therapy, and 29 of these patients were removed from the study after the initial course of MMC. The median number of treatments received was 1.7 in the SD group and 1.9 in the LD group.

The lower dosage regimen resulted in fewer hematologic and nonhematologic toxic effects. Specifically, significantly less Grade 3 or 4 leukopenia, granulocytopenia, thrombocytopenia, and anemia occurred. The nonspecific side effects of chemotherapy did not change as dramatically, and the incidence of pulmonary and hemolytic uremic syndromes was too small for meaningful comparisons.

Unfortunately, although there were fewer toxic effects, disease progression did not allow the administration of more therapy; therefore, remission duration, time to progression, and survival were not prolonged significantly. Because few patients responded and the study was terminated early, this study does not have the statistical support to assert an advantage for one approach *versus* the other.

In a few patients with progressive disease, re-treatment with SD recaptured a response, and in two patients the response resulted in significant remissions of 21 months or longer and 30 months.

Table 6. Re-Treatment With Standard Doses of Patients Who Had Disease Progression at Low Doses (n = 9)

Initial response (no.)	Subsequent response (no.)
CR (2)	CR (1) 21+ mo MR < 6 wk
PR (3)	PD (3)
SD (4)	SD (2) 3, 4 mo PD (1) PR (1) died of toxic effects at 30 mo

CR: complete response; MR: minor response; PR: partial response; PD: progression; SD: stable disease.

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