Mitomycin C and mitoxantrone chemotherapy for advanced breast cancer: efficacy with minimal gastrointestinal toxicity and alopecia*

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Summary. In an attempt to examine the possibility of decreased toxicity in patients with advanced breast cancer who had not previously received chemotherapy, 33 women were given combination chemotherapy consisting of mitomycin C (10 mg/m^2) every 6 weeks and mitoxantrone (6 mg/m^2) every 3 weeks. The patients had predominantely visceral disease and received a median of two cycles of therapy. Of the 32 evaluable subjects, 15 (47%) achieved a partial response lasting a median of 7 months. Hematological toxicity was generally mild, although there were two episodes of sepsis. One patient developed hemolytic-uremic syndrome, and one subject developed pulmonary fibrosis, both presumably attributable to treatment with mitomycin C. Another patient died of hepatic failure (hepar lobatum). Thus, there were five patients who sustained life-threatening toxicities; this may have been due to the poor performance status and advanced age of some of the patients. Gastrointestinal toxicity and alopecia were minimal. Patient acceptance was high and there was an improvement in symptomatology in the majority of patients. In conclusion, mitomycin C and mitoxantrone chemotherapy is an active drug combination for the treatment of advanced breast cancer that seldom causes significant distressing gastrointestinal side effects or alopecia; however, the duration of response to this regimen appears to be shorter than that obtained with either cyclophosphamide – methotrexate – 5-fluorouracil (CMF) or cyclophosphamide – Adriamycin – 5-fluorouracil (CAF) combination chemotherapy.

Introduction

Although considerable progress has been achieved in the treatment of metastatic breast cancer, a plateau in the response rate and duration of response has been apparent with a wide variety of combination chemotherapy regimens [4, 7, 8, 13, 14, 21, 22]. The response rates vary between 40% and 70%, with a median duration of response of ≤ 1 year. Newer approaches using high-dose chemotherapy plus autologous bone marrow transplantation and/or human HSFs (hematopoietic growth factors) are under investigation [10, 16]. The majority of patients with metastatic breast cancer are treated with conventional combination chemotherapy such as CMF (cyclophosphamide, methotrexate and 5-fluorouracil) or CAF (cyclophosphamide, Adriamycin and 5-fluorouracil). These combination regimens produce distressing side effects, including gastrointestinal disturbances and hair loss. Although decreasing the dose intensity of these drug combinations may reduce the incidence of side effects, it obviously also results in diminished efficacy [20].

Mitoxantrone is an anthracenedione whose structure and spectrum of activity are similar to those of Adriamycin. Mitoxantrone alone has been reported to produce a response rate of 33% in previously untreated breast cancer patients [19]. The antitumor activity of mitoxantrone as a single agent is similar to that of Adriamycin, but nausea, vomiting, alopecia, and stomatitis occur significantly less frequently with mitoxantrone [1, 19].

Mitomycin C, an antitumor antibiotic that leads to the alkylation and cross-linking of DNA produces a 35% response rate in patients with metastatic breast cancer. However, the duration of response to this drug is short-lived ($\leq$ 3 months). Its predominant side effect is delayed cumulative myelosuppression; vomiting and hair loss are not major toxicities [9].

The most effective combination therapy involving mitomycin C is that with Adriamycin; however, use of the latter drug results in vomiting and hair loss [12]. In a search

for effective combination chemotherapy with minimal gastrointestinal toxicity and alopecia, we studied the efficacy of mitomycin C and mitoxantrone in patients with advanced breast cancer.

Patients and methods

A total of 34 patients with histologically proven advanced breast cancer were entered in the study. One patient was ineligible because her abdominal disease proved to be ovarian cancer. All patients had measurable disease except four subjects with bony disease, two of whom had baseline carcinoembryonic antigen (CEA) levels of ≥ 100. Eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 3, a life expectancy of ≥ 12 weeks, and adequate peripheral blood counts; moreover, the only prior drug treatment allowed was adjuvant chemotherapy. The starting doses were 10 mg/m^2 i.v. mitomycin C every 6 weeks and 6 mg/m^2 i.v. mitoxantrone every 3 weeks; both drugs were given by rapid push injection. As an antiemetic, patients generally received only 10 mg i.v. dexamethasone on day 1. Baseline studies included history and physical examination, determination of ECOG performance status, tumor measurements, complete blood count (CBC), biochemical profile, determination of CEA levels, and appropriate radiographic and imaging studies. The CBC, biochemical profile and CEA were repeated every 3 weeks. Tumor response and drug toxic effects were graded according to World Health Organization (WHO) criteria [11]. The duration of partial response was measured from the 1st day of treatment to the date of the first observation of progressive disease.

Patients were considered to be evaluable for assessment of improvement in performance status if their pretreatment status showed some extent of impairment. Likewise, subjects were evaluable for symptomatic improvement if they had experienced pretreatment symptoms.

Results

The clinical characteristics of the 33 patients are shown in Table 1. The median age of our patients was higher than that in many other series. Approximately 55% of the subjects had visceral dominant disease and a performance status of 2 or 3. No patient had received prior chemotherapy for metastatic breast cancer. Most subjects had undergone two different hormonal manipulations prior to receiving chemotherapy and were clearly no longer responding to treatment with hormones. Of the seven patients who had not received hormonal therapy, four had visceral crises (lymphangitic lung disease or liver metastases) and three had estrogen receptor-negative tumors. The 33 patients were given a median of two cycles, with one cycle representing 6 weeks of treatment (range, 1–7 cycles). At least 80% of the projected optimal dose was delivered in 88% of the mitomycin C courses and in 83% of the mitoxantrone courses.

Table 1. Patient characteristics

	Patients (n)
Total	33
Median age (range)	64 (38–82) years
Performance status:	
0	2
1	13
2	11
3	7
Dominant site of disease:	
Soft tissue	7
Bone	7
Visceral	19
Prior therapy:	
Hormones (advanced disease or adjuvant)	26
Adjuvant chemotherapy	12 (5 CMF, 6 L-PAM, 5-FU, 1 Cyclo-Adria)[a]

[a] 3 of these patients relapsed within 6 months of completing adjuvant therapy. CMF, cyclophosphamide-methotrexate-5-fluorouracil; L-PAM, melphalan; 5-FU, 5-fluorouracil; Cyclo-Adria, cyclophosphamide-Adriamycin

Table 2. Response to mitomycin C and mitoxantrone in 32 evaluable patients according to the site of disease

Site of disease	Responders/total number of patients
Liver	6/6
Lungs/pleura	5/11
Soft tissues (skin, subcutaneous, nodes and breast)	3/13
Bones	7/17

One patient was not evaluable for response because she died within 3 weeks of starting treatment. In all, 15 subjects achieved a partial response (47% of evaluable patients; 95% confidence interval, 30%–68%); there were no complete responses. Responses were obtained in all disease sites (Table 2). However, <25% of patients with soft-tissue disease responded, whereas all subjects with liver metastases sustained a partial response. The median duration of partial response was 7 months (range, 2+–14+ months). There was no difference in the average performance status of responders versus nonresponders (1.7 vs 1.5, respectively). The median survival for the entire group was 9 months (range, 1–32+ months). Four patients are still alive at 4, 14, 16 and 32 months of follow-up.

Hematological toxicity encountered with this drug combination was largely attributable to the chronic and cumulative effects of mitomycin C therapy. The median WBC and platelet counts demonstrated a cumulative effect that was attributable to mitomycin C treatment (Table 3). Two patients had persistent thrombocytopenia after three and five doses of mitomycin C; both developed persistent thrombocytopenia concomitant with disease progression in the liver or bones. One patient died of bilateral pneumonia and leukopenia (WBC = 1,700/cm^3) within 3 weeks of starting chemotherapy. Another subject was hospitalized with leukopenia and sepsis. One patient developed hemolytic-uremic syndrome, presumably associated with mitomycin C, but recovered after therapy with plasmapheresis and aspirin. Two additional subjects had abnormally low serum haptoglobin levels, and mitomycin C was discontinued. Only one patient required a platelet transfusion.

Nonhematological toxicity was generally mild (Table 4). The vast majority of patients had minimal hair loss and mild gastrointestinal disturbances. There were two unusual toxic reactions. One patient with moderately severe chronic obstructive lung disease developed a marked

Table 3. Median WBC and platelet counts

	Course 1:		Course 2:		Course 3:		Course 4:		Course 5:	
	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22
WBC count	6,700	4,000	4,500	4,900	4,100	3,400	3,500	2,800	3,700	2,400
Platelet count	294,000	205,000	270,000	150,000	212,000	121,000	142,000	68,000	121,000	64,000

Table 4. Nonhematological toxic effects

WHO grade	Hair loss	Nausea and vomiting
0	25 (76)[a]	17 (52)[a]
1	7 (21)	13 (39)
2	-	2 (6)
3	1 (3)	1 (3)

[a] Number of patients (%)

Table 5. Palliative effects

	Number of patients/total evaluable
Improvement in symptoms	21/32 (66%)
Improvement in performance status	9/29 (31%)
Weight gain of $\geq$ 5%	3/27 (11%)

diminution in her carbon monoxide-diffusing capacity that was presumably attributable to treatment with mitomycin C. Another patient died of severe liver failure and bleeding varices; at autopsy, hepar lobatum that was presumably due to the chemotherapy was found [17].

An assessment of the quality of life of our patients was done (Table 5). Most subjects reported a subjective improvement in symptoms, but only 31% showed evidence of an improvement in performance status.

Discussion

The rationale for conducting this trial of combination chemotherapy was to obtain effective therapy with minimal toxicity. The response rate and duration of response for the mitomycin C and mitoxantrone regimen are probably somewhat inferior to those reported for cyclophosphamide-methotrexate-5-fluorouracil (CMF) or cyclophosphamide-Adriamycin-5-fluorouracil (CAF) combination chemotherapy [3, 7]. However, patient acceptance was high as noted in the quality of life assessment. Moreover, gastrointestinal toxicity and hair loss were minimal and hematological toxicity was acceptable. However, three patients developed unusual toxicities (hemolytic-uremic syndrome, diffuse lung disease, and hepar lobatum) in the initial part of the fourth cycle, and at least two of these toxicities have previously been associated with mitomycin C therapy [15, 18]. Hepar lobatum has been associated with several types of chemotherapy [17]. A prospective randomized trial should be conducted to determine whether mitomycin C and mitoxantrone chemotherapy is as efficacious as CMF chemotherapy and, at the same time, more acceptable to patients.

Since the treatment of metastatic breast cancer is palliative, low-dose chemotherapeutic regimens that result in fewer gastrointestinal disturbances and less hair loss have been developed [6]. However, recent studies suggest that these low-dose or intermittent combination regimens may result in inferior response rates and survival [5, 20]. The current study demonstrates that myelosuppressive chemotherapy can be delivered with minimal gastrointestinal toxicity and alopecia. A study of this regimen in previously treated patients reported similar minimal nonhematological toxicity [2]. Combination therapy using drugs that result in minimal gastrointestinal toxicity and alopecia can increase patient acceptance and have a less adverse effect on the quality of life of these patients; furthermore, dose escalation with concomitant hematopoietic growth factor (HSF) therapy may increase the efficacy of such treatment without a concomitant increase in its toxicity to patients.

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