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Mitomycin C, melphalan and methotrexate combination chemotherapy for palliation of disseminated breast cancer

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Summary. *Fifty-seven patients with metastatic breast carcinoma have been treated with mitomycin C (10 mg/m² IV 6-weekly), melphalan (6 mg/m² PO × 3 days, 3-weekly), and methotrexate (35 mg/m² IV 3-weekly) to assess the efficacy and toxicity of this regimen. Of 48 evaluable patients 19 (40%) responded for a median period of 5 months and 12 (25%) had stabilisation of disease. Of the 12 patients previously treated with adriamycin only one responded, whereas 18 of the 36 patients without previous chemotherapy responded. Although healing of bone metastases was infrequent control of hypercalcaemia was commonly seen. Generally the treatment was well tolerated and treatment was stopped in only five patients because of toxicity. Cumulative marrow toxicity was observed but was not a significant problem in the first 6 months of treatment. Mitomycin C, melphalan, and methotrexate (MMM) appears to provide an effective, well tolerated chemotherapy combination for metastatic breast carcinoma.*

Introduction

Patients with metastatic breast carcinoma who are treated with combinations of cytotoxic agents commonly show a response rate of 40%–60% [1] but this is not achieved without significant toxicity. Many cytotoxic combinations contain adriamycin and cyclophosphamide, which frequently produce alopecia, gastrointestinal upset, weight loss [8] and, in the case of adriamycin, cardiomyopathy. These drugs usually produce little more than symptomatic relief and transient tumour regression and so there are sound reasons for evaluating cytotoxic combinations which may have similar efficacy but less toxicity.

Drugs which show useful activity against metastatic breast carcinoma without major symptomatic toxicity include mitomycin C [1, 9], methotrexate [1], and melphalan [1]. We have combined all three in an attempt to provide an effective palliative treatment for disseminated breast carcinoma. Although mitomycin C and melphalan are both alkylating agents they do not show cross resistance in experimental systems [3].

Patients and methods

Fifty-seven patients with metastatic breast cancer were treated with MMM between December 1981 and February 1983. Three patients were premenopausal and 54 postmenopausal and the mean age of all patients was 59 years (range: 34–83 years). The mean Karnofsky performance status before treatment was 85 with a range of 60–100 and the mean disease-free interval was 34 months with a range of 0–168 months. There were 12 patients who had previously received chemotherapy, and 37 had received hormone therapy. All patients had assessable disease but only 48 of the 57 had an adequate trial of therapy (the administration of two complete cycles of MMM or disease progression after one cycle) and were therefore evaluable. Of the nine patients who were not evaluable five withdrew from therapy because of toxicity and four died within 3 months of entry into the study. All patients were assessed for toxicity at 6-week intervals. Response to treatment was assessed using UICC criteria [4]. A response was recorded when unidimensional lesions decreased by at least 50% and, for bidimensional lesions, when the product of perpendicular diameters decreased by at least 50%. Recalcification of osteolytic lesions was interpreted as a response in bone. Responses had to be maintained for at least 2 months.

Prior to treatment with MMM all patients had clinical examination, haematology and biochemistry profiles, chest X-ray, and radiographic skeletal survey performed. During the first cycle of treatment the haematology profile was repeated weekly and thereafter 3-weekly. Clinical examination was performed every 6 weeks and X-rays and biochemistry profiles were repeated 3-monthly or more frequently as required. Other investigations performed for specific indications included bone and liver scintigraphy, liver ultrasonography, and bone marrow examination.

A complete cycle of MMM covered 42 days with mitomycin C given on day 1, methotrexate on days 1 and 21, and melphalan on days 1–3 and 21–23. Doses were as follows: mitomycin C 10 mg/m² IV bolus; methotrexate 35 mg/m² IV bolus, and melphalan 6 mg/m² PO daily for 3 days. Folinic acid rescue was used only if significant methotrexate-related toxicity occurred.

Results

Of 48 patients evaluable for response two achieved a complete remission and 17 a partial remission, giving a response rate of 40% (Table 1). (The overall response rate in the 57 treated patients was 33%.) Of these evaluable patients, 12 achieved stabilisation of disease, leaving 17 patients (34%) whose disease progressed despite treatment. There were 36 patients with symptoms at the beginning of MMM treatment, 21 of

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whom (58%) experienced subjective benefit from treatment. Patients who had not received previous chemotherapy had a better response rate of 50%, whereas only one of 12 patients previously treated with chemotherapy (adriamycin plus vinca alkaloid) responded. The median duration of response and disease stabilisation was 5 months and 4 months, respectively.

The pattern of response by metastatic site is shown in Table 2. Although lymph node metastases showed a 42% response rate the response in other soft tissue sites was less impressive. Liver metastases showed a surprisingly high response rate of 56%, five of nine responses being complete. The low response rate of bone metastases probably reflects the difficulty of assessing bone tumour response, and it is perhaps significant that 51% of patients with bone metastases achieved stabilisation. In addition, 14 patients reported improvement in bone pain yet only one of these patients demonstrated objective improvement in bone metastases. Hypercalcaemia is another manifestation of bone metastases and MMM reversed hypercalcaemia in all six patients with this complication (Table 3).

The toxicity produced by MMM was mainly haematological and gastrointestinal. There were no treatment related deaths. Vomiting during at least 50% of treatment courses occurred in 31% of patients, but most found this tolerable and only two withdrew from treatment for this reason. Leukopenia was a more frequent manifestation of haematological toxicity than thrombocytopenia and the doses of mitomycin C and melphalan were frequently reduced to avoid marrow toxicity (Table 4). Marrow depression was seldom severe, and only two patients ceased treatment because of persistently low blood counts. Cumulative marrow toxicity with repeated courses of MMM was seen (Table 4) but the effect was severe in few cases. The frequency of neutropenia (< 3 and $> 1 \times 10^9$/l) rose from 27% after course 1 to 60% after course 4, and thrombocytopenia (< 100 and $> 20 \times 10^9$/l) from 8% to 50% after courses 1 and 4, respectively. Severe leukopenia ($< 1 \times 10^9$/l) and thrombocytopenia ($< 20 \times 10^9$/l) occurred rarely but were associated with a prolonged recovery period.

Table 1. Overall response rate

	All treated patients	Patients evaluable for response
No. of patients	57	48
No. of treatment courses given	1–7 (mean 2.8)	1–7 (mean 3.1)
Complete response	2 (4%)	2 (4%)
Partial response	17 (30%)	17 (35%)
No change	12 (21%)	12 (25%)
Progressive disease	17 (30%)	17 (36%)
Complete plus partial responses	19 (33%)	19 (40%)
Patients not evaluable	9 (15%)	–

Response rate with previous chemotherapy 1/12 (8%)
Response rate without previous chemotherapy 18/36 (50%)
Median duration of response 5 months
Median duration of disease stabilisation 4 months

Table 2. Response to MMM by site

Disease site	No. of patients	Complete responses	Partial responses	No change	Progressive disease	CR + PR (%)
Nodes	12	5	0	4	3	5 (42)
Other soft tissue	25	1	6	13	5	7 (28)
Lung	7	1	1	4	1	2 (28)
Pleura	9	0	3	5	1	3 (33)
Bone	23	0	4	12	7	4 (18)
Liver	16	5	4	4	3	9 (56)
Abdomen (other than liver)	3	0	0	2	1	0 (0)

Table 3. Hypercalcaemia control with MMM

	Ca^{2+} when MMM commenced	Time to achieve normocalcaemia (days)	Duration of normocalcaemia (days)
Patient 1	3.33 mmol/l	55	57
Patient 2	3.37 mmol/l	66	38+
Patient 3	3.47 mmol/l	40	90+
Patient 4	3.21 mmol/l	17	90+
Patient 5	4.80 mmol/l	7	96+
Patient 6	3.79 mmol/l	3	17+

Table 4. Cumulative marrow toxicity in 57 patients treated with MMM

	MMM course no.			
	1	2	3	4
WBC < 3 and $> 1 \times 10^9$/l	27%	30%	36%	60%
$< 1 \times 10^9$/l	3%	0%	4%	0%
Platelets < 100 and $> 20 \times 10^9$/l	8%	17%	20%	50%
$< 20 \times 10^9$/l	2%	0%	4%	0%
Patients with dose reduction because of marrow toxicity	–	4%	42%	67%
Average mitomycin C dose given (% of ideal dose)	–	91%	82%	60%
Average melphalan dose given (% of ideal dose)	–	83%	79%	66%

Discussion

Although breast carcinoma is a chemosensitive tumour, long-term survival following chemotherapy for disseminated disease is depressingly rare. In addition, combination chemotherapy does not improve the overall survival of patients with disseminated disease [7], and palliation remains the most realistic goal of treatment. It is therefore important that the toxicity of treatment does not exceed the symptomatic benefit from tumour regression. Mitomycin C, methotrexate, and melphalan in combination produce an acceptable response rate of 40% with modest toxicity. In addition, 25% of patients achieved disease stabilisation (usually stabilisation of bone metastases) and 58% derived subjective benefit from treatment. Although objective improvement of bone metastases was rarely seen bone pain was commonly relieved.

Most previous studies using mitomycin C-containing regimens have included a high proportion of cases previously treated with cytotoxic agents, and response rates have varied between 9% and 58% [2, 5, 6, 10], with median response durations of 4–8+ months. There is a general correlation between mitomycin C dosage and response rate but there seems little advantage in exceeding a dose of 10 mg/m^2. In this study all patients pretreated with chemotherapy had received adriamycin plus a vinca alkaloid, and the poor response rate with MMM in this group suggests cross resistance between mitomycin C and adriamycin. However, patient numbers are too small to allow definite conclusions.

An unexpected aspect of MMM treatment was the high response rate in liver metastases, but more cases with liver metastases treated with MMM will be necessary to confirm this trend. Although the objective response rate in bone metastases was poor it can be assumed that MMM doses have activity in bone, because bone pain was frequently relieved and hypercalcaemia secondary to bone metastases was very effectively controlled. Long-term control of metastatic hypercalcaemia has not been documented with chemotherapy other than mithramycin. It is possible that mitomycin C has a similar hypocalcaemic effect to mithramycin.

Subjective toxicity from MMM was mild, and those patients who had previously received adriamycin-containing regimens generally preferred MMM. A distinct advantage of MMM over combinations containing adriamycin or cyclophosphamide is the absence of alopecia. Mitomycin C and melphalan both produce cumulative marrow toxicity, and mitomycin C in particular is known to produce progressive thrombocytopenia [6, 10]. In this study marrow toxicity was not a major problem in the first 6 months of treatment, although cumulative marrow toxicity was seen and necessitated frequent dose reduction. One patient achieved complete remission after three cycles of MMM and was then treated with high-dose melphalan and autologous marrow transplant. The neutropenic period after melphalan was very prolonged and it is possible that MMM had compromised marrow stem cell function. There were no cases of pulmonary toxicity or microangiopathic haemolytic anaemia secondary to mitomycin C in this study.

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