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Mitomycin C and Vinblastine in the Treatment of Advanced Breast Cancer

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Abstract—*Forty-nine women with progressive metastatic breast cancer, extensively pretreated, received mitomycin C* 12 mg/m^2 *and vinblastine* 6 mg/m^2 *intravenously every* 3 weeks. *Eleven patients responded, giving a response frequency of* 22%. *Considering only the* 40 *patients evaluable after two or more courses of treatment, the response frequency is* 27.5%. *Responses occurred predominantly at soft tissue sites. Subjective toxicity was mild.*

INTRODUCTION

ABOUT 30% of patients with advanced breast cancer achieve a regression with mitomycin C [1–5]. Vinblastine also has some activity, giving a response rate of nearly 20% [2, 6, 7]. Synergism between the two drugs has been found *in vitro* [8], so there is good reason to test the combined use of these drugs *in vivo*.

In 1978, Denefrio *et al.* [9] reported a phase II study of mitomycin C 6 mg/m^2 and vinblastine 5 mg/m^2 given on day 1 of a 2-week cycle to 17 women who had had previous cytotoxic drugs. Subjective toxicity was minimal, but there was only one partial remission (PR) in 14 evaluable patients. Later, Konits *et al.* [10] reported a response rate of 40% using mitomycin C 20 mg/m^2 on day 1 and vinblastine 0.15 mg/kg on days 1 and 21 of a 6- to 8-week cycle. Toxicity, however, was severe, with 32% of patients (and 20% of treatment courses) affected by infection requiring hospital treatment, and 10% of patients requiring blood or platelet support for haemorrhage at some stage during chemotherapy.

We report here a trial to further evaluate mitomycin C and vinblastine (MMC and VBL) in patients with progressive metastatic breast cancer after prior standard chemotherapy.

PATIENTS AND METHODS

Forty-nine women (median age, 58 yr; range, 35–81 yr) with histologically proven progressive metastatic breast cancer were studied. All had previously received at least one regimen of chemotherapy (either doxorubicin, mitoxantrone or a combination of cyclophosphamide, methotrexate and 5-fluorouracil) and 19 had been treated with two or more regimens. In addition, 35 had received various endocrine treatments, 19 had undergone radiotherapy to sites of metastatic disease and eight had received alpha-interferon. No patient had received hormonal therapy in the 2 months before starting MMC and VBL, nor chemotherapy for at least 3 weeks.

All patients had at least two sites of metastatic disease (either cutaneous, lymphatic, breast, liver or lung) and 12 had four or more involved sites. Forty-five patients had some soft tissue involvement (lymphatic, breast or skin) and half had visceral disease (lung or liver).

Eligibility criteria included the presence of evaluable disease, a total white blood cell count (WBC) of $>4.0 \times 10^9$/l and a platelet count of $>120 \times 10^9$/l.

Mitomycin C 12 mg/m^2 (maximum 20 mg) and vinblastine 6 mg/m^2 (maximum 10 mg) were given by slow intravenous injection on day 1 of a 21-day cycle. Subsequent courses were given according to the day 22 blood count, with 50% dose reductions if the WBC was between 2.0 and 3.99×10^9/l or if the platelet count was between 70 and 119×10^9/l. If the counts were lower than 2.0×10^9/l (WBC) or 70×10^9/l (platelets), treatment was postponed until haematological recovery had occurred.

Assessment for objective response as defined by Hayward *et al.* [11] was made before each course of chemotherapy and treatment continued until the onset of progressive disease (PD). Toxicity was recorded for each course and graded according to WHO criteria [12].

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RESULTS

Of the 49 patients entered into the trial, 40 were evaluable for response after two or more courses of treatment, five died within 2 weeks of the first course, two developed PD after the first course (dying at 4 and 5 weeks) and two were withdrawn after the first course due to toxicity.

Eleven patients responded, including one complete response (CR) lasting 9 weeks in a woman with cutaneous and breast metastases. Ten patients had partial response (PR), with a median duration of 21 weeks (range 9–40 weeks). This is an overall response rate of 22% (11/49 patients entered), or 27.5% of evaluable patients who received two or more courses of treatment.

Responses occurred predominantly in metastases at soft tissue sites (particularly cutaneous), with only two objective responses in 21 instances of skeletal and 13 cases of pulmonary involvement (Table 1). No responses were seen in 14 patients with hepatic disease.

Subjective toxicity was mild (Table 2) and generally the treatment was preferred to previous chemotherapy regimens. One patient aged 74 was withdrawn from the trial after the first course because of grade 3 nausea and vomiting, but 21 had symptoms graded 2 or less and 17 did not experience any nausea or vomiting. Only seven patients developed any degree of alopecia, and this was never more severe than grade 2. Neurological toxicity as indicated by constipation occurred in four patients on treatment, but none had paresthesiae or postural hypotension. Four patients developed symptoms or signs of possible pulmonary hypersensitivity to mitomycin C (cough or dyspnoea with transient parenchymal shadowing on chest radiograph), but all recovered following cessation of chemotherapy and a short course of prednisolone. Treatment was subsequently reintroduced at half dosage in one patient without further ill effect. Four subjects experienced mild transient diarrhoea and three described other effects (malaise for 48 hr in one, erythema in one and generalized pain in one).

Haematological toxicity was also mild, with a median lowest day-22 WBC count of 3.9 × 10^9/l (range, 2.5–23.3 × 10^9/l), and no infections requiring antibiotics were recorded. The median lowest day-22 platelet count was 160 × 10^9/l (range 26–461 × 10^9/l) and there were no episodes of haemorrhage, but two patients were withdrawn from treatment because of prolonged thrombocytopenia (after 1 and 4 courses respectively). It is not known whether either of these patients had tumour infiltration of the bone marrow, but both had bone metastases in addition to soft tissue and visceral involvement.

Table 1. Response according to site

Site	No. of patients	Response
Skin	35	12 (5 CR)
Breast	32	7 (3 CR)
Lymphatic	27	7 (4 CR)
Bone	21	1
Liver	14	0
Lung	13	1

Table 2. Toxicity from mitomycin C and vinblastine (WHO criteria)

	No. of patients affected	Grade 1	2	3
Alopecia	7	5	2	0
Nausea and vomiting	23	11	10	2*
Neurological	4	0	4	0
Pulmonary†	4	0	3	1
Diarrhoea	4	4	0	0
Other‡	3	—	—	—

*Resulted in cessation of treatment after one course in one patient.

†Drugs re-introduced at 50% dosage in one; withdrawn permanently in three.

‡Malaise for 48 hr in one, generalized erythema in one and generalized pain for 5 days in one.

DISCUSSION

The aim of chemotherapy in advanced breast cancer is to achieve effective palliation of progressive symptomatic disease. This trial tested the combination of mitomycin C and vinblastine in a group of previously extensively treated women with a considerable burden of metastatic disease. The drugs were administered on a simple 21-day cycle at a dosage approximately midway between those described by Denefrio *et al.* [9] and Konits *et al.* [10].

The overall response rate was 22% (or 27.5% of patients evaluable after two or more courses). Disease affecting soft tissue sites was the most responsive (Table 2), while the response of visceral and bone metastases was poor. These findings are similar to those of Garewal *et al.* [13], who reported a 32% response rate in 22 evaluable patients treated with a similar schedule of mitomycin C 10 mg/m^2 (monthly for two cycles then 6-weekly) and vinblastine 5mg/m^2 (fortnightly for two cycles then 3-weekly), although they reported greater success with disease at visceral sites.

The treatment was generally well tolerated, but four patients experienced reversible pulmonary symptoms, possibly attributable to mitomycin C hypersensitivity, and two developed prolonged thrombocytopenia (although the possible role of

bone marrow infiltration is not known in these cases). There were, however, no episodes of bleeding or infection, which affected 10 and 30% respectively of the patients treated by Konits *et al.* [10] using 20 mg/m^2 of mitomycin C.

This study confirms that the combination of mitomycin C and vinblastine is an active regimen in advanced breast cancer, although the observed response rate appears to be no greater than for mitomycin C used as a single agent [1–5]. In view of the low acute subjective toxicity, it is worth considering for use earlier in the clinical course of the disease if contraindications to other chemotherapy regimens exist.

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