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Short communication

A phase II trial of mitomycin C and 5-fluorouracil as second-line therapy in advanced breast cancer

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Summary. Fifty five patients who had relapsed or progressed from chemotherapy for advanced disease were treated with mitomycin C and 5-FU on a 6 weekly regimen. After a median of 2 cycles of therapy the overall response rate was 12% with no complete responses. Significant leucopenia but no thrombocytopenia was seen and despite the low overall response rate the regimen was tolerable and did produce responses in patients primarily resistant to Adriamycin combination chemotherapy. Low overall activity indicates the need for more effective second line treatment.

Introduction

Chemotherapy in advanced breast cancer produces relatively high response rates of around 50%–55% in previously untreated patients, which increase to 70%–80% with more intensive regimens [3]. However, responses are often short-lived and second-line treatment is less successful, with the therapeutic benefit of cytotoxic chemotherapy being highly questionable in many cases. In an attempt to control relapsed breast cancer without exacerbating previous toxicity, we performed a phase II study of the combination of 5-fluorouracil (5-FU) and mitomycin C (MMC). 5-FU has well-established activity [4] and MMC, although not as thoroughly studied, has demonstrated activity when given in combination with 5-FU [5, 7] and other drugs; in the latter regimens the individual contribution of MMC is less clear [2, 4, 6].

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Patients and methods

A total of 55 patients with advanced breast cancer had measurable disease and 51 had progressed or relapsed after previous chemotherapy. All received 6 mg/m^2 MMC every 6 weeks and 1 g/m^2 5-FU every 3 weeks. Patients were considered to be evaluable for response after completion of one full cycle of treatment, i.e. one dose of MMC and two doses of 5-FU. Therapy was continued until relapse or documentation of progressive disease, or until toxicity demanded dose reductions to ineffective levels.

Results

The patients' characteristics are listed in Table 1. In all, 50 patients were evaluable for response. Five patients failed to complete one cycle; two died of progressive disease; one died of gastrointestinal haemorrhage (haemorrhagic gastritis with residual breast cancer in the breast and liver at post-mortem examination); and treatment was discontinued in two cases because of clinical toxicity. A median of 2 cycles of therapy was given (range, 1–6 cycles). An overall response rate of 12% (6/50) was obtained (95% confidence interval, 5%–24%), comprising no complete responses and 6 partial responses (median duration of response, 144.5 days; range, 35–286 days). However, 14 of these patients received only 1 course. One response was seen in the liver and all others occurred in soft-tissue or nodal disease. A further nine patients showing no objective change reported symptomatic improvement in bone pain and/or reduced dyspnoea.

The toxicity of the therapy was documented in 39 patients who received more than one treatment. Table 2 shows that nausea and vomiting of grade 0–1 occurred in 36 patients; alopecia was noted in 2 individuals; and mild to moderate lethargy was the most important side effect. Significant leucopenia was recorded in 23 patients but there were no serious infections; significant thrombocytopenia was not observed. Myelosuppression resulted in the removal of two patients from the study before completion of the first cycle.

Table 1. Patients' characteristics at study entry

Mean age	52 (range, 33–74) years	
Performance status:		
0	5	
1	30	
2	15	
Not recorded	5	
Menopausal status:		
Premenopausal	14	
Postmenopausal	37	
Not stated	4	
Oestrogen receptor status:		
ER +	12	
ER –	25	
Unknown	18	
Sites of disease:		Dominant site:
Soft tissue	38	22
Nodes	20	0
Lung	15	9
Pleura	9	3
Liver	16	16
Bone	13	4
Other	2	1
Previous hormone treatment:		
Tamoxifen		36
Aminoglutethimide		9
Megestrol acetate		9
Previous chemotherapy		51
Mean number of cycles		6.7 (range, 3–21)
Previous doxorubicin		42
Response to initial chemotherapy:		
No change		11
Progression		17
Refractory		16
Non-evaluable		8

Table 2. Toxicity

	Grade			
	0	1	2	3
Nausea/vomiting	31	5	3	3
Diarrhoea	41	1	0	0
Constipation	40	1	1	0
Alopecia	39	1	0	2
Lethargy	34	4	1	3
Leucopenia	16	7	13	10

Discussion

This study shows that the combination of MMC and 5-FU gives a low response rate when used as second-line treatment in advanced breast cancer. Our cohort was an unselected group of patients with a variety of patterns of metastatic disease. Five patients who received only one course of treatment probably had inherently resistant disease or very rapidly progressive disease. Many of our patients had previously been treated (with varying response) with doxorubicin, and this has been shown to be the most important prognostic factor in predicting response to second-line therapy [1]. However, the six patients who did show a response received the present treatment as second- or third-line treatment; furthermore, three of these six subjects had not responded to prior chemotherapy, including two who had been given doxorubicin as front-line therapy. Thus, the MMC-5-FU combination is sometimes active in cases that are resistant to standard chemotherapy. Subjective toxicity was usually mild. We recognised the likelihood of the occurrence of severe neutropenia as a potential complication of MMC therapy in this heavily pretreated population. In any event, nearly 60% of our patients developed significant leucopenia even at the present low dose of MMC. Without extra support measures there seems to be little scope for escalation of the dose of this drug in this group of patients.

Most studies using regimens containing MMC as second-line chemotherapy have also included doxorubicin, vinca alkaloids and alkylating agents in varying combinations [2, 6, 7]. Such drug combinations incorporating MMC have produced response rates ranging from 32% to 52% [3]. In comparison, two studies using MMC and 5-FU [5, 7] produced response rates of 58% and 12%; the first investigation [5] included previously untreated patients, and the second used a relatively small dose of 5-FU (400 mg/m^2) every 5 or 6 weeks. Using a higher dose of 5-FU, we obtained the same response rate in the present study.

MMC and 5-FU in combination have little activity in previously treated, advanced breast cancer, although 'primary resistant' patients may occasionally respond. Generally, however, more effective therapies are required in such cases.

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