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Mitozantrone and Methotrexate Chemotherapy With and Without Mitomycin C in the Treatment of Advanced Breast Cancer: a Randomised Clinical Trial

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Patients with advanced breast cancer were randomised to 3M (mitozantrone 6.5 mg/m²q 21 days, methotrexate 30 mg/m²q 21 days, mitomycin C 6.5 mg/m²q 42 days) or 2M (as 3M but without mitomycin C). The objective response rates of 30% in 51 evaluable patients receiving 3M and 26% of 54 patients receiving 2M were not significantly different. 4/16 patients not responding to 2M responded to 3M on crossover. Both regimes were well tolerated but there was significantly less haematological toxicity and fewer dose reductions and delays with 2M. We conclude that patients should initially be treated with 2M and that non-responding patients should be crossed to 3M.
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INTRODUCTION

THE COMBINATION of mitozantrone, methotrexate and mitomycin C was developed as a well-tolerated chemotherapy regime which would effectively palliate advanced breast cancer [1]. In a comparison between this regime (3M) and a vincristine, anthracycline and cyclophosphamide combination (VAC) there was a 53% overall response rate [complete response (CR) and partial response (PR)] in patients receiving 3M compared with 49% in patients receiving VAC [1,2]. The 3M regime was remarkably well tolerated in comparison with VAC, with a very low incidence of alopecia and stomatitis and no neuropathy. However, haematological toxicity with the 3M regime was significant, being the principal reason for the dose modification necessary in 65% of patients. We felt that mitomycin C caused much of the haematological toxicity. We have, therefore, carried out a randomised study to compare the response and toxicity of the 3M regime with an identical therapy which does not contain mitomycin C (2M) in patients with advanced breast cancer.

PATIENTS AND METHODS

Patients with histologically or cytologically proven advanced breast cancer who had progressive disease were eligible. Patients were excluded if they had received previous treatment with any of the cytotoxics used in the study. Patients treated with 3M received mitozantrone 6.5 mg/m² and methotrexate 30 mg/m² 3-weekly and mitomycin C 6.5 mg/m² 6-weekly. The doses of mitozantrone and methotrexate were identical in the 2M regime. Folinic acid was not given routinely. Dose reductions were made where the day 21 leucocyte count was 3.0–3.5 × 10^9/l and delays where the leucocyte count was less than 3.0 × 10^9/l or the platelet count was less than 100 × 10^9/l. Patients were fully staged at entry and on completion of treatment. Response was determined according to standard UICC criteria [3]. Subjective toxicity from each treatment cycle was assessed by questionnaire. The nadir leucocyte and platelet count were systematically determined during cycle 1, and as clinically indicated on subsequent cycles. Toxicity scores (on the WHO scale [4]) for each parameter were taken as the worst score recorded throughout treatment by each individual patient. The χ^2 test was used for the analysis of categorical variables (overall response and haematological toxicity).

RESULTS

114 patients were randomised between March 1987 and May 1990, 56 to 3M and 58 to 2M. 7 patients were excluded from the analysis for the following reasons: 4 patients with breast cancer were randomised in error and in 3 patients, the primary site of cancer was in doubt. Of the 107 eligible patients, 2 (1 in each arm) were randomised but not treated, 52 received 3M and 55 received 2M. Characteristics of the patients were similar in the two groups with respect to age [mean (SD) years; 3M: 61.8 (11.9), 2M: 61.2 (12.3)], menopausal status (post, 3M: 45, 2M: 46), Karnofsky score (< 70; 70–80; 90–100, 3M: 14, 29, 9; 2M: 12, 25, 18), disease-free interval [mean (SD) months; 3M: 41 (53),2M: 40 (40)], interval from first metastases to entry [mean (SD) months; 3M: 11 (14), 2M: 20(18)] and presence of liver metastases (3M: 14, 2M: 15). 46 patients in the 3M arm had received endocrine therapy (20 > one treatment) for advanced disease compared with 44 (26 > one treatment) in the 2M arm. 12 of these patients (3M:6, 2M:6) had previously received one course of chemotherapy (in 11 for advanced disease).

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Number of courses of treatment and dosage

Of the 105 treated patients, 25 in the 3M arm had four or more courses of treatment compared with 27 in the 2M arm. The remaining 26 patients in the 3M arm and 27 in the 2M received one to three courses. The proportion of patients initially receiving less than 80% of the target dose of at least one drug was 12.8% for 3M and 13.5% for 2M; these reductions were made because of age, impaired renal or liver function, or reduced bone marrow reserve.

Response rate

Table 1 details the response. 8 patients were classed as not assessable for the following reasons; 2 died within 2 weeks of entry from their disease, 3 were lost to follow-up, 1 had a fatal myocardial infarction after two cycles and 2 were not formally reassessed clinically before treatment was changed. The response rate of assessable patients in the 3M arm was 30% [95% confidence interval (CI), 17–45%) compared with 26% in the 2M arm (95% CI, 15–40%) a difference in response rates of 4% (95% CI, 14–22%; $P = 0.85$). 7 patients had previously responded to other chemotherapy of whom 3 (2M:1, 3M:2) were amongst the responders in this study. The median duration of response was 31 weeks overall (range 20–46); this was not different in the two arms of the study. The median survival in the two arms was 9 months for 3M and 10.5 months for 2M.

Crossover

16 patients who were randomised to the 2M regime and who either had progressive disease [12] or stable disease without symptomatic improvement [4] after between two and four treatment cycles were crossed over to 3M. 4 of these patients then achieved a partial response and in a further 4, the disease stabilised.

Table 1. Response

	3M	2M
Overall Response	$n = 51$	$n = 54$
CR	0	1
PR	14	12
	14 (30%)	13 (26%)
NC	9	13
PD	24	24
	33	37
NA	4	4
Local/chest wall	$n = 23$	$n = 26$
CR/PR	3	5
NC/PD	15	17
NA	5	4
Soft tissue	$n = 16$	$n = 25$
CR/PR	3	9
NC/PD	9	10
NA	4	6
Bone	$n = 28$	$n = 25$
CR/PR	5	4
NC/PD	12	12
NA	11	9
Visceral	$n = 28$	$n = 31$
CR/PR	4	4
NC/PD	14	21
NA	10	6

CR = complete response; PR = partial response; NC = no change; PD = progressive disease; NA = not assessable; n = no. of patients.

Table 2. Toxicity

		Severity (WHO grade) 0	1	2	3	4
Leucocytes*	3M	6	9	17	11	9
	2M	20	20	8	4	2
Platelets	3M	41	6	2	2	0
	2M	48	1	2	2	0
Alopecia	3M	36	10	5	0	0
	2M	43	3	6	2	0
Nausea and vomiting	3M	31	8	9	3	0
	2M	32	9	10	3	0
Stomatitis	3M	37	5	5	4	0
	2M	46	4	3	1	0
Constipation	3M	49	1	1	0	0
	2M	51	1	2	0	0
Diarrhoea	3M	49	0	1	1	0
	2M	50	2	2	0	0
Lethargy	3M	32	4	10	5	0
	2M	35	6	11	2	0

*Chi-square test for trend: $P < 0.001$.

Toxicity

Toxicity data are summarised in Table 2. Haematological toxicity was the main reason for dose reductions and treatment delays, which occurred in significantly more 3M patients than 2M patients (19 vs. 9; $P = 0.031$). Hospitalisation with febrile neutropenia was significantly more common in the 3M arm, occurring in 12 patients at some stage of treatment compared with only 3 in the 2M arm ($P = 0.014$). 5 of the 16 patients crossed over from 2M to 3M experienced severe neutropenia during 3M treatment. In the majority of these cases, no reduction of drug doses was made on crossover. In later crossover patients, a 20% dose reduction was therefore made. Non-haematological toxicity was similar in the two arms, although stomatitis and lethargy tended to be more troublesome in patients receiving the 3M regime. There were no patients with complete alopecia in the 3M regime and only 2 in the 2M regime. There was a single episode of cardiotoxicity observed in a patient who received 2M.

DISCUSSION

This study shows that the 3M regime is more toxic than 2M and that the principal toxicity of 3M, that of myelosuppression, can be greatly reduced by omitting mitomycin C. In agreement with the previous reports of 3M chemotherapy [1,2,5] we have confirmed the acceptability of the regime and have demonstrated that of 2M, particularly in respect of a low incidence of alopecia, emesis and stomatitis. Both the 2M and 3M regimes gave similar response rates, although some patients who failed to respond to 2M treatment subsequently responded to the addition of mitomycin C. We, therefore, do not feel that out results justify the use of the 3M regime as first line chemotherapy for advanced breast cancer and that patients requiring cytotoxic therapy should, at least initially, be treated with the 2M regime.

The response rate in our study is lower than in the previous reports of 3M [1,2,5]. A particular factor which may be relevant is that the majority of our patients had been heavily pretreated with endocrine therapies. Recently, Tannock *et al.* [6] have argued that patients who have received previous endocrine therapy have a reduced response rate to chemotherapy and a shortened duration of effect of chemotherapy. This may be

applicable to our patients. Other factors which are likely to have contributed to our low response rate are the relatively advanced age of our patients in comparison with those in the two previous reports (Powles *et al.*, 1991: mean age 55; Jodrell *et al.*: mean age 51) and the significant proportion of patients in our study with a Karnofsky score < 70. In consequence, we have used a slightly reduced target dose of all three drugs in our schedule in comparison with previous reports.

Our own studies [7,8] and those of others [9] have shown that locally advanced breast cancer responds well to mitozantrone-containing chemotherapy. Thus, Mansi *et al.* [9] reported a 60% response rate in locally advanced breast cancer. Gazet *et al.* [8] using the 3M regime found 16/30 patients (53%) achieved a response. This previously untreated category of patients may respond as well to the 2M regime with less toxicity.

In conclusion, we feel that patients with advanced breast cancer should receive the less toxic 2M regimen as first-line cytotoxic therapy and only if no response is seen should mitomycin C be added to the regime. Haematological toxicity should be monitored carefully in patients who receive the 3M regime.

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Phase II Study of High-dose Epirubicin and Etoposide in Advanced Non-small Cell Lung Cancer

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25 consecutive patients with advanced non-small cell lung cancer (NSCLC) were treated with high-dose epirubicin (HDE) 135 mg/m² and etoposide 60 mg/m² (days 1–3) every 3 weeks. 121 courses, (median 6, range 1–7), were administered and evaluable for toxicity: WHO grades III/IV leukocytopenia in 60/36 (80%) courses, thrombocytopenia in 18/6 (20%) and grades II/III anaemia in 31/6 (31%). Median (range) left ventricular ejection fraction (LVEF) fell from 63% (53–73, $n = 25$) to 60% (48–73 $n = 16$) after 5 courses ($P < 0.02$). 2 patients had a drop of more than 15% in LVEF with an epirubicin dose of 675 mg/m². Apart from 1 patient who had tachycardia 6 months after the last course, no patient had congestive heart failure. There were 2 complete and 7 partial responses [total 9/25 (36%, 95% confidence interval: 18–57.5%)]. Median survival is 31.8 (4.3–75) weeks. Combination HDE and etoposide in NSCLC offers no advantage over HDE alone and is more toxic.
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INTRODUCTION

THE PROGNOSIS of patients with advanced non-small cell lung cancer (NSCLC) remains poor and requires development of active drug regimens. Recently, high-dose epirubicin (≥ 120 mg/m²) as a single agent was found to have significant antitumour activity in NSCLC. Response rates in five studies varied from 17% to 36%, while toxicity was moderate [1–5]. Among other active single agents in NSCLC producing partial response rates exceeding 15% is etoposide [6, 7]. In this study we report on the efficacy of the combination of HDE and etoposide in advanced NSCLC.

In December 1989, a dose-range finding study was started with the aim of finding a safe dose for the combination of HDE and etoposide. The first 6 patients were treated with epirubicin