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The Importance of Dose Scheduling With Mitoxantrone, 5-Fluorouracil and Leucovorin in Metastatic Breast Cancer

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We have studied a mitoxantrone, 5-fluorouracil (5-FU) and leucovorin chemotherapy regimen in metastatic breast cancer. 8 patients received mitoxantrone 10 mg/m^2 on day 1, leucovorin 200 mg/m^2 and 5-FU 300 mg/m^2 on days 1–5 by intravenous bolus every 28 days in a pilot study. Grades 3–4 granulocytopenia followed 55% of the courses, with 2 patients admitted for febrile neutropenia. Only a 29% objective response rate was seen in a subsequent phase II trial using reduced mitoxantrone doses. Comparison with other trials suggested that 5-day bolus 5-FU administration adversely affects the combination's therapeutic index.

Key words: breast cancer, metastatic, chemotherapy
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INTRODUCTION

THE COMBINATION chemotherapy of metastatic breast cancer with mitoxantrone, 5-fluorouracil (5-FU) and leucovorin has been studied in at least seven different clinical trials [1–7]. The potential interest of combining these agents comes from the observations that both mitoxantrone [8–10] and 5-FU/leucovorin [11–14] are active as second-line therapy of metastatic breast cancer, there is no known mechanism of cross-resistance between them, and they have moderate and different toxicity profiles. Each study used different dose schedules, and response rates ranged from 33 to 65%. Interestingly, the toxicity profile was mild in all studies except one, where 75% of the patients had grade 3–4 leucopenia with six episodes of neutropenic sepsis and 19% grade 3–4 thrombocytopenia [3]. Furthermore, these severe side-effects were only associated with a 33% response rate. This clinical trial was the only one in which both 5-FU and leucovorin were administered for 5 consecutive days by intravenous (i.v.) bolus every 4 weeks, suggesting the possible impact of dose scheduling with this chemotherapy combination. We now report another trial in metastatic breast cancer, which confirms the toxicity and relative lack of efficacy of mitoxantrone, 5-FU and leucovorin administered in a similar dose schedule.

PATIENTS AND METHODS

Eight women with evaluable metastatic breast cancer and no prior chemotherapy, except as adjuvant therapy completed more

Table 1. Mitoxantrone, 5-FU/leucovorin trials in metastatic breast cancer

	Hainsworth [1]	Jones [2]	Swain [3]	Carmo-Pereira [4]	Despax [5]	Gardin [6]	Graziane [7]	Jolivet (this paper)
Patient numbers	35	57	16	32	58	33	12	34
Regimen (mg/m²)	q 3 weeks	q 3 weeks	q 4 weeks	q 3 weeks	q 4 weeks	q 1 week	q 3–4 weeks	q 4 weeks
Mitoxantrone	12 i.v. D1	10 i.v. D1	10 i.v. D1	8 i.v. D1	7–15 i.v. D1	4 i.v. D1	10 i.v. D1	5–7.5 i.v. D1
Leucovorin	300 1h infusion D1–3	100 i.v. D1–3	500 i.v. D1–5	400 i.v. 2h infusion D1 and 8	200 i.v. D1–5	150 i.v.	20 i.v. D1–3	200 i.v. D1–5
5-FU	350 i.v. push D1–3	1000 continuous i.v. infusion D1–3	375 i.v. bolus D1–5	500 i.v. bolus D1 and 8	350–450 2h infusion D1–5	370 i.v.	1000 continuous i.v. infusion D1–3	300 i.v. bolus D1–5
Toxicity	2% grade 4 neutropenia	No severe toxicity	Severe muscositis and leucopteia	No severe toxicity	No severe toxicity	15% grade 3 neutropenia	No severe toxicity	55%≥ grade 3 neutropenia in pilot study
Response rate (%)	65	45	33	65	59	33	50	29

q, once every; i.v., intravenous; D, day.

than 6 months previously, were first entered on a pilot study. They could have received prior hormonotherapy as adjuvant therapy or for metastatic disease. Initial chemotherapy doses were mitoxantrone 10 mg/m² by i.v. bolus on day 1, 5-FU 300 mg/m² by i.v. bolus, immediately preceded by leucovorin 200 mg/m² by i.v. bolus on days 1 to 5. Cycles were repeated every 28 days. Thirty-four women with measurable metastatic breast adenocarcinoma, and satisfying the same entry criteria as for the pilot study, were subsequently registered onto a phase II study. Malignant pleural effusion, ascites, bone metastases and lymphangitic lung metastases were not considered measurable. Patients with known cerebral metastases were excluded. Other entry criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, expected life expectancy > 8 weeks, granulocyte count $> 2 \times 10^9$/l, platelet count $> 100 \times 10^9$/l and no cardiac risk factors. All patients gave written informed consent before entering the study. 20 patients had only one site of metastatic disease, with two sites in 9 patients, and more than two sites in 5 patients. Only 4 of the 15 patients treated with adjuvant chemotherapy had received doxorubicin-containing regimens.

In the phase II trial, treatment was administered as in the pilot study except that mitoxantrone was started at 5 mg/m² by i.v. bolus on day 1 with 2.5 mg/m² increments if the granulocyte nadir was $\geq 2 \times 10^9$/l in the preceding course or 2.5 mg/m² decreases if the granulocyte nadir was $< 0.75 \times 10^9$/l. The daily 5-FU dose was decreased by 50 mg/m² in the next treatment course if grade 2 or 3 diarrhoea or oral mucosal toxicity occurred. The leucovorin dose was not modified. Cycles were repeated every 28 days until disease progression was documented.

Patients were monitored at each visit for clinical response and toxicity which was assessed according to the WHO grading system. Abnormal radiological studies were repeated once every 8 weeks. A complete response was defined as complete disappearance of all lesions for ≥ 8 weeks and a partial response as a $\geq 50\%$ reduction in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum of 8 weeks with no new lesions.

RESULTS

Thirty-eight cycles of chemotherapy were administered to 8 patients with metastatic breast cancer in the pilot study. Grade 3–4 granulocytopenia followed 55% of administered courses with 2 patients necessitating admission for febrile episodes. Gastro-intestinal toxidity was mild. 2 patients had complete disappearance of bone and subcutaneous metastases, and 2 others had significant improvement in pleural, bone and lymph node disease. The 4 other patients progressed on therapy.

A total of 169 courses of chemotherapy were administered in the phase II study. A median of five courses were given to each patient (range 1–13). Mitoxantrone doses could only be increased by one to two 2.5 mg/m² dose increments in 41% of the administered courses, while 5-FU had to be decreased in 34%. There were very few episodes of severe toxicity, with only one episode of grade 3 granulocytopenia, two grade 3 diarrhoea, one grade 3 mucositis and seven grade 3 alopecia in the 169 courses administered. One patient had multiple venous small bowel thromboses with necrosis following two chemotherapy courses, and required small bowel resection, following which she rapidly deteriorated and died. All patients were assessable for response: 3 (8.8%) had complete and 7 (20.6%) partial responses to therapy for a total response rate of 29.4% (95% confidence interval of 14–44%).

DISCUSSION

The different dose schedules of mitoxantrone, 5-FU and leucovorin reported in metastatic breast cancer are summarised in Table 1. The most significant differences between regimens are in the 5-FU administration schedules which have varied from weekly bolus, days 1–3 2-h or continuous infusions, to days 1–5 bolus administration. These dose schedule differences can

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have profound effects on 5-FU pharmacokinetics and toxicity [15]. Significant toxicity after administration of mitoxantrone, 5-FU and leucovorin was only seen in the clinical trial by Swain and colleagues [3] and in our pilot study, the only two studies in which 5-FU was administered in five daily bolus injections. Furthermore, response rates in these two trials were amongst the lowest reported. While the reduced dose of mitoxantrone used in our phase II study may have been an important contributing factor to the poor response rate observed, the 33% response rate reported by the Swain group cannot be explained by dose reductions. The reasons underlying the adverse interactions of 5-day bolus 5-FU/leucovorin with mitoxantrone are unknown, but this administration schedule should be avoided.

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