the 4 cases (4.6%) of mixed response reported here were seen among the 87 ptients treated between 1991 and 1994. The mechanism underlying the occurrence of mixed response can only be speculated on. Whether different clones of tumour cells have a different sensitivity to chemotherapy, which in turn may be related to proven differences between tumour cells in overexpression of P-glycoprotein [6], remains to be elucidated. However, other, yet unknown factors may be as important. Although mixed response to chemotherapy for soft tissue sarcomas remains a rare experience, physicians should be aware of the possibility of this type of response.

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Mitoxantrone, 5-Fluorouracil and Leucovorin in Metastatic Breast Cancer

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THE DRUG regimen containing mitoxantrone, 5-fluorouracil and leucovorin (MFL), first described by Hainsworth and associates [1] has been widely applied in metastatic breast cancer [2–10]. We report our results with this regimen since the responses in our study in anthracycline-pretreated patients differ from other published data [1–3, 7–10].

We treated 33 patients with metastatic breast cancer with the MFL regimen as first- to fourth-line chemotherapy, consisting of mitoxantrone (12 mg/m^2 intravenous (i.v.) bolus on day 1), 5-fluorouracil (350 mg/m^2 i.v. bolus on days 1–3) and leucovorin (300 mg over 1 h before 5-FU, i.v. on days 1–3), repeated every 3 weeks. In the case of leucopenia $< 3000/\mu l$ or thrombocytopenia $< 100\,000/\mu l$, chemotherapy was delayed for 1 week. If there was no recovery, the dose of mitoxantrone was reduced to 75%. If further toxicity occurred in subsequent courses, stepwise reduction by 25% of the initial mitoxantrone dose was performed. Because of age (> 70 years), toxicity from previous chemotherapy or extensive radiotherapy in 9 patients, the initial mitoxantrone dose was set at 9 mg/m^2 and reductions as above were applied. Response was evaluated after two or three cycles and again after five or six cycles if no progression occurred. 31 patients were evaluable: treatment was first-line in 11, second-line in 12, third-line in 7 and fourth-line in 1 patient. There were 9 patients who had previously received anthracycline treatment, and MFL was third-line therapy for most of those (7/9). 2 patients, not evaluable for response due to protocol violation, are included in the report on toxicity. Evaluable patients' characteristics and their response to MFL are shown in Table 1.

32% (10/31) of patients (95% confidence interval: 15–48%) showed an objective response, all partial. 42% (13/31) had stable disease and 26% (8/31), all heavily pretreated patients, had progression. Of the evaluable patients receiving 9 mg/m^2 mitoxantrone from the start, two were partial responders, three had stable disease and 3 had progressive disease. When MFL was used as first-line therapy, the response rate was 72%. In the subgroup of patients receiving MFL as second-line therapy only, without previous anthracyclines, the response was reduced to 18%. No response was seen after an anthracycline-based chemotherapy for metastatic disease. The mean duration of response was 7 months (range 4–10) from the start of treatment. Toxicity (WHO criteria), being assessed in 164 chemotherapy cycles, was generally mild, with myelosuppression causing a dose reduction in 24% of cycles. Alopecia grade 3 was never recorded. Nausea and/or vomiting appeared in 13% of patients.

This report on MFL reveals the benefits and major limitations of the regimen. Toxicity is limited. The overall respone rate of 32% is lower than the 65% reported by Hainsworth and associates [1], due to differences in patients' selection. Indeed, Hainsworth's group preferred MFL as second-line therapy. Only 6% of those patients had previous anthracycline treatment for metastatic disease, never within 6 months from MFL, whereas in our evaluable population, 29% had previous anthracyclines of which one-third had received this within 6 months.

Compared with studies of only anthracycline-pretreated patients, with responses from 38 to 59% [2, 3, 7–10], our 0% response in this subgroup is strikingly low. It remains to be proven that bolus instead of infusional 5-fluorouracil administration accounts for this poor response, as suggested by Jolivet and associates [4]. We conclude that MFL is a well tolerated and active regimen as first-line therapy for metastatic breast cancer. Previous treatment with anthracyclines compromises the response rate of the regimen and should, therefore, be avoided.

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Table 1. Patients' characteristics (and response to MFL)

Total no. of evaluable patients	31
Mean age in years	55, range 38–82
Oestrogen receptor content of primary tumour	
Positive	9
Negative	5
Unknown	17
Dominant site of metastasis	
Visceral (liver or lungs)	18
Bone exclusive	6
Soft tissue	7
Previous treatment for metastatic disease (response to MFL)	
None	2 (2 PR)
Radiotherapy and/or hormonal	9 (6 PR, 3 SD)
Chemotherapy (CMF) without anthracycline	11 (2 PR, 6 SD, 3 PD)
Anthracycline-based chemotherapy:	
Within 6 months before MFL	3 (3 PD)
More than 6 months before MFL	6 (4 SD, 2 PD)

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; PR, partial response; SD, stable disease; PD, progressive disease; MFL, mitoxantrone, 5-fluorouracil, leucovorin.

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Recombinant Granulocyte Colony Stimulating Factor in the Treatment of Small Cell Lung Cancer: A Long-term Follow-up

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CELL LINES derived from solid tumours can show an enhanced proliferative response when grown in the presence of haemato-

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