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# Mitoxantrone, Leucovorin and High-dose Infusional 5-Fluorouracil: an Effective and Well-tolerated Regimen for the Treatment of Advanced Breast Cancer

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**Mitoxantrone and 5-fluorouracil (5-FU) are active drugs with a favourable toxicity profile in advanced breast cancer. The activity of 5-FU can be enhanced by modulation with leucovorin. Continuous infusion of 5-FU yields a superior activity with less toxicity compared with bolus injections. 27 patients with advanced breast cancer, 22 of them pretreated, received intravenous (iv) mitoxantrone, 14 mg/m², day 1, iv leucovorin, 300 mg, days 1 and 15, and 5-FU, 4 g, 48-h infusion, days 1 and 2, 15 and 16, once every 28 days (MLF regimen). Leucovorin was administered either as a bolus prior to the 5-FU infusion or mixed together with the 5-FU during the first 24 h. There were 12 partial responses, 9 patients had stable disease, and 5 had progressive disease. 1 patient was not evaluable because of concomitant irradiation of the target lesion. The overall response rate was 46%; for previously untreated patients it was 100% and for pretreated patients it was 33%. Grade 3 nausea/vomiting was noted in 7 evaluable patients (26%) and grade 4 haematological toxicity in 1 patient (4%). Only 1 patient had complete alopecia. The median duration of response was 13 months in untreated, and 12 months in pretreated patients. It was concluded that MLF is an active regimen in advanced breast cancer, even in highly pretreated patients, with moderate and manageable toxicity. Assessment in first-line treatment appears to be of interest.**
**Key words: breast cancer, chemotherapy, MLF**
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## INTRODUCTION

METASTATIC BREAST cancer cannot be cured with current therapeutic manoeuvres. Chemotherapy will be administered to the majority of patients with advanced disease for temporary palliative relief, and in this setting a low toxicity profile is of interest. Mitoxantrone is an effective agent with myelosuppression as the main toxic effect, while nausea/vomiting, mucositis, alopecia and cardiotoxicity are less pronounced than with anthracyclines [1]. 5-Fluorouracil (5-FU) is another active drug, and its activity can be enhanced by modulation with leucovorin [2, 3]. In colon cancer, continuous infusion of 5-FU has a superior activity, with low toxicity and virtually no myelosuppression, compared with bolus injections [4, 5]. Intermittent continuous infusion with high-dose 5-FU is particularly active with extremely low toxicity in colorectal cancer [6], but has not been assessed in breast cancer. Therefore, we conceived the MLF regimen (mitoxantrone, leucovorin, 5-fluorouracil) which combines these drugs, taking advantage of their activity as single agents, with low non-overlapping toxicity, and particularly incorporating intermittent continuous infusion with high-dose 5-FU. We utilised fixed doses of 5-FU/leucovorin because our intention was to administer 5-FU at a higher dose intensity than can be achieved with bolus injections (i.e. over 800 mg/m²/week), and because the optimal dose of leucovorin to produce the most effective potentiation of 5-FU, especially of infusional 5-FU, is unknown.

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## PATIENTS AND METHODS

Eligibility criteria included histologically proven breast cancer, performance status 0–3, measurable/evaluable lesions and adequate organ functions, especially normal ejection fraction in case of pretreatment with anthracyclines. Extent of pretreatment and time interval between last chemotherapy and the initiation of MLF were no exclusion criteria.

Mitoxantrone was administered at a dose of 14 mg/m², day 1 intravenously (iv), leucovorin, 300 mg, days 1 and 15 iv and 5-FU, 4 g, 48-h infusion, days 1 and 2, 15 and 16, once every 28 days (MLF regimen). Leucovorin was administered either as a bolus prior to the 5-FU infusion or mixed together with the 5-FU during the first 24 h. After the first cycle, most patients were treated ambulatory via port-attached portable pumps. With a portable pump, the leucovorin had to be administered as a bolus prior to the 5-FU. Treatment had to be continued until progression or severe toxicity, but the maximal number of cycles was limited to six. Thereafter, chemotherapy was either discontinued or continued with leucovorin 300 mg and 5-FU 1000 mg bolus iv, fixed doses, once every 3 weeks.

Definitions of measurability, response and toxicity were assessed according to WHO criteria. For evaluable patients with bone metastases only, partial response (PR) was defined as an estimated 50% reduction of pathological uptake on bone scans with > 50% decrease in tumour marker and clear improvement in symptoms and general condition. Response duration was calculated from the start of treatment.

## RESULTS

A total of 27 patients were treated. Only 5 were previously untreated. 4 were previously treated with one to two hormonal

*Table 1. Patients' characteristics* (n = 27)

| | |
|---|---|
| Median age (years) | 53 (range 33–78) |
| Median performance status | 1 (range 0–3) |
| Median body surface area ($m^2$) | 1.7 (range 1.4–1.8) |
| Median no. of metastatic sites | 2 (range 1–4) |
| Soft tissue | 14 |
| Bone | 15 |
| Visceral | 11 |
| Central nervous system (irradiated) | 2 |
| Previously untreated | 5 |
| Pretreated | 22 |
| Hormones only | 4 |
| Chemotherapy (±hormones) | 18 |
| Anthracyclines | 14 |
| Adjuvant | 5 |
| Advanced | 9 |
| Non-anthracyclines | 4 |
| Adjuvant | 1 |
| Advanced | 3 |

drugs only, and 18 with one or more chemotherapy regimens (median 1, range 1–3) plus or minus hormonal agents. 14 of these 18 patients were pretreated with anthracyclines. The median age was 53 years (range 33–78) and median performance status was 1 (range 0–3). The median number of metastatic sites was two (range one to four). Metastatic sites were soft tissue (52%), bone (56%; 26% bone metastases only), visceral (41%) and central nervous system (7%). In Table 1, a summary of the patients' characteristics is shown.

*Toxicity*

The median number of courses was six (range one to six). Toxicity was low, mainly nausea/vomiting which was generally not severe. Haematological toxicity was virtually absent. Treatment postponement was not mandatory in any case. There was no clinically significant mucositis nor diarrhoea. A summary of the toxicity is outlined in Table 2. 1 patient had complete alopecia, the others experienced only slight alopecia without necessitating a wig.

*Response*

26 patients were evaluable. There were 12 PR, 9 (35%) patients had stable disease, including 1 patient with progression during treatment with epirubicin and cyclophosphamide, and 5 patients had progression. 1 patient was not evaluable because of concomitant irradiation of the target lesion. The overall response rate was 46%; for previously untreated patients it was 100% and for pretreated patients it was 33%. All patients who qualified as

*Table 2. Toxicity* (124 *cycles*)

| | | No. of patients |
|---|---|---|
| Nausea/vomiting | WHO grade 0 | 17 |
| | grade 2 | 2 |
| | grade 3 | 8 |
| Leucopenia | WHO grade 3 | 13 |
| | grade 4 | 1 |
| Alopecia | WHO grade 0–2 | 26 |
| | grade 3 | 1 |

*Table 3. Response* (n = 27)

| | No. of patients |
|---|---|
| PR | 12 |
| SD | 9 |
| Early death | 1 |
| PD | 4 |
| Not evaluable | 1 |
| Overall response rate | 12/26 (46%; 95% confidence interval 29–64.5%) |
| Previously untreated | 5/5 (100%) |
| Pretreated | 7/21 (33%; 95% confidence interval 17–55%) |

PR, partial response; SD, stable disease; PD, progressive disease.

responders had symptomatic relief, more than 50% decrease in the tumour marker CA 15-3 (in cases elevated at start of treatment) and patients with performance status of 1 to 3 had an increase in performance status by at least one level. 2 patients with performance status of 3 improved to a status of zero. The relatively small number of patients in this trial precludes more definite analysis of response in subgroups.

The median duration of response in previously untreated patients was 13 months (response 4, 7, 13, 16+ and 16+ months), and in pretreated patients 12 months (range 8–24).

*Survival*

After a median follow-up of 16 months, a total of 18 patients have died and 9 are still alive. The median survival of all patients was 14 months (range 1–24+ months).

## DISCUSSION

The response rate, duration of response and survival in this study with mostly pretreated patients is quite high. Especially for this category of patients, a low toxicity profile, including only slight alopecia, is of paramount interest. Leucovorin, by either bolus or continuous infusion, combined with 5-FU bolus injections has been used for advanced breast cancer, producing a 17–24% response rate, with 3–5 months median duration of remission when used as salvage treatment [7, 8] and 48% response rate with only 4 months median time to progression in first-line treatment [9]. Toxicity, especially myelosuppression and mucositis, were substantial in these trials.

Similar results to ours have been reported in two other studies with the same combination of drugs, although with different doses and schedules. In the first study, of 31 patients pretreated either adjuvantly or for metastatic disease, 20 (65%) achieved a response with a median duration of 6 months. In that trial, 5-FU and leucovorin were administered as bolus injections and myelosuppression was the main side-effect [10]. In the second study, 24 (45%) of 53 patients, pretreated for metastatic disease, achieved a response with a median duration of 6 months [11]. These authors utilised bolus injections of leucovorin and 72 h continuous infusion of 5-FU, 1 g/$m^2$ daily, once every 3 weeks, a schedule which is quite similar to ours. They reported mucositis as the most frequent side-effect, with mild myelosuppression.

The overall response rate in second-line treatment in these two trials plus our study was 51/105 (49%), and in patients pretreated with anthracyclines, either adjuvantly or for metastatic disease, 23/60 (38%).

A French trial, reported in abstract form, with a schedule similar to the trial from Vanderbilt, yielded a response of 50% in

26 anthracycline-pretreated patients, and of 69% in 23 previously untreated patients [12].

By employing continuous infusion of 5-FU, a high dose intensity can be achieved without significant myelosuppression, while the incidence of other toxicities such as mucositis depends on the duration of the infusion. Whereas the dose intensities of mitoxantrone were only slightly different in the four studies, the dose intensities of leucovorin/5-FU were different, respectively, 250/500 [12], 175/350 [10], 100/1000 [11] and approximately 88/1200 mg/m$^2$/week (median surface area 1.7 m$^2$, Table 1) in our trial. These figures suggest that a high dose intensity of 5-FU compensates for less dose intense leucovorin.

In conclusion, the MLF regimen, employing continuous infusion of high dose 5-FU, is a useful regimen for second-line palliative treatment of metastatic breast cancer. This regimen warrants assessment in first-line treatment, possibly with an even higher dose intensity of leucovorin/5-FU.


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# Phase I/II Study of Low-dose Intravenous OKT3 and Subcutaneous Interleukin-2 in Metastatic Cancer

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**In a phase I/II study the safety, immunostimulatory and antitumour effects of a combined OKT3/interleukin 2 (IL-2) treatment was studied in 15 cancer patients who failed IL-2 treatment. OKT3 was given as a 2-h intravenous infusion. Doses of 50, 100, 200 and 400 μg OKT3 were studied. Within 24 h, subcutaneous IL-2 was started 5 days/week for 4 weeks, at a dose of 9–18 × 10$^6$ U daily. Maximum tolerated dose was 400 μg OKT3 with neurotoxicity as dose-limiting toxicity. Toxicity of subcutaneous IL-2 was acceptable. At the maximum tolerated dose, 9 patients with renal cell carcinoma with measurable disease were treated in a phase II setting. 8 patients were evaluable for response. 4 patients had stable disease and 4 had progressive disease. An increase of activated lymphocyte subpopulations could not be found, although OKT3 was detectable on lymphocytes *in vivo*. Only if laboratory studies shed light on methods of improving immunostimulating effects of OKT3 will further clinical studies be warranted.**
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## INTRODUCTION

AFTER DISAPPOINTING results with non-specific stimulation of the immune system with Bacillus Calmette-Guérin or specific stimulation with tumour-derived vaccines [1], the use of recombinant cytokines has opened up a new approach in the immunotherapy of disseminated cancer. Objective responses in selected tumours have been observed using interferon or interleukin-2 (IL-2). Renal cell carcinoma (RCC) and malignant melanoma (MM) appear to be the most susceptible to this strategy. Interferons have shown an overall response rate of approximately