Mitomycin C, 5-fluorouracil and folinic acid (Mi-Fu-Fo) as salvage chemotherapy in breast cancer patients with liver metastases and impaired hepatic function: a phase II study

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Patients with measurable liver metastases due to breast cancer and elevated liver enzymes were enrolled into the study. The planned schedule was mitomycin C 8 mg/m^2 on day 1, 5-fluorouracil 750 mg/m^2 and folinic acid 300 mg/m^2 on day 1and 2 every 4 weeks (Mi-Fu-Fo). Between May 1998 and December 2002, 30 patients with a median age of 51 years (range 33–74) were enrolled. All of them suffered from extensive metastases of the liver resulting in liver dysfunction. Myelosuppression was the most frequent toxicity. Six patients had a partial remission, 12 patients had stable disease and 12 patients progressed during treatment. The median time to progression was 4.5 months in all patients and 7.0 months in patients who responded to the therapy. The median overall survival for the total population was 6.0 months and in the group of responding patients 12.0 months. Mi-Fu-Fo, therefore, provides a valid option for breast cancer patients with liver dysfunction due to liver metastases. ***Anti-Cancer Drugs*** **15:719–724**
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Introduction

Major aims of a palliative treatment in metastatic breast cancer patients are to obtain disease control, diminish symptoms and to guarantee a good quality of life [1]. The treatment of metastatic breast cancer after failure of taxanes and anthracyclines remains controversial, as the benefit is not well determined and may be limited by the toxicity [2]. However, sequential application of a variety of treatments has considerably improved the outcome of metastatic breast cancer in the last 25 years [3].

Extensive liver metastases combined with liver dysfunction is usually considered as the terminal stage of disease with a short survival time. No standard therapeutic option exists as most chemotherapies need a sufficient liver function with liver enzymes not elevated above $\geq 3\times$ upper normal limit (UNL) or $>1.5\times$ UNL associated with an elevated alkaline phosphatase (AP; $\geq 2.5\times$ UNL), if they should be used with a standard dosage [4]. Even in this unpromising situation patients ask for every treatment option and are willing to accept therapies even with low success rates.

Mitomycin C has been a treatment option for metastatic breast cancer since the early 1980s [5]. It belongs to the family of antitumor antibiotics. The plasma half-life is 1–2 h and may be prolonged in patients with hepatic dysfunction [6]. In an earlier investigation no alterations in pharmacologic parameters related to liver dysfunction, dose, and concomitant cytotoxic drugs could be found [7]. Several trials have been published using mitomycin C in combination regimens. Mitomycin C is especially effective in hypoxic tumor cells [8] and therefore an interesting drug. The acute toxicity profile is comparable with other cytotoxic agents, and consists of neutropenia and thrombocytopenia. Chronic toxicities such as renal failure due to the development of hemolytic uremic syndrome (HUS) or pulmonary toxicity are infrequent, but may be severe, and therefore an upfront use of mitomycin should be avoided. The combination of mitomycin C with 5-fluorouracil (5-FU) and folinic acid was used before with promising results [9].

The objective of this study is to establish a feasible chemotherapy regimen for patients with metastatic breast cancer and severely impaired liver function due to hepatic metastases.

Patients and methods

Study design and patients

Between May 1998 and December 2002, 30 patients with metastatic breast cancer involving the liver were

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prospectively included in a phase II study (Table 1). Further inclusion criteria were as follows: bidimensionally measurable disease, elevated liver enzymes $> 1.5 \times$ UNL and AP $\geq 2.5 \times$ UNL or liver enzymes $\geq 3 \times$ UNL, normal hematological values (WBCs $\geq 3 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; hemoglobin ≥ 10 g/dl), normal renal function. There were no restrictions regarding previous treatment for breast cancer. There were no restrictions for a low performance status or life expectancy. Written informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki.

Treatment plan

All patients received a 4-week cycle of Mi-Fu-Fo chemotherapy. The regimen consisted of mitomycin C, (8 g/m^2, 15 min i.v. infusion) on day 1 and folinic acid (300 mg/m^2, i.v. bolus) plus 5-fluorouracil (750 mg/m^2, i.v. bolus) on days 1 and 2. Prednison 50 mg was given orally throughout days 1–5 to prevent pulmonary toxicity [10].

All patients received dexamethasone 8 mg i.v. and ondansetron 8 mg i.v. as premedication for nausea on day 1 and 2. Prophylactic recombinant colony stimulating growth factor was not given.

Assessment of symptoms and side-effects was made at the beginning and end of every cycle. Blood cell counts and values of blood chemistry were controlled weekly or more often if clinically indicated.

The treatment plan consisted of 6 cycles unless there was evidence of progressive disease or severe toxicity. There was no planned dose modification. If the WBC was $< 2 \times 10^9$/l or the platelets $< 100 \times 10^9$/l on day 29 the subsequent cycle was delayed for 1 week. If non-hematological severe (grade IV) toxicities occurred, the treatment was to be discontinued.

Patient and treatment evaluation

Tumor response was evaluated in 23 patients every second cycle of therapy using computed tomography scanning or ultrasound according to WHO criteria. Seven patients died after the first cycle, probably as a consequence of progressive disease.

The time to progression (TTP) and overall survival were calculated from the start of treatment until progression occurred or until death by any cause using the Kaplan–Meier test. Toxicity and tolerability analyses were performed on all patients who completed at least one complete cycle of therapy (4 weeks). Hematological and non-hematological toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Table 1 Patient characteristics

No. of patients	*n*
Liver dysfunction	30
$\geq 1.5 \times$ UNL + AP	30
$\geq 2.5 \times$ UNL	2
$\geq 3 \times$ UNL	28
hyperbilirubinemia	17
Patients with ascites	10
Age [years (median)]	51 (33–74)
ECOG performance status (median)	2 (0–4)
Mi-Fu-Fo cycles ($n = 109$)	4 (1–9)
No. of previous chemotherapy regimens	
0	3
1	6
≥ 2	21
No. of previous hormone therapies	
0	11
1	8
2	6
≥ 3	5
Metastatic sites	
liver	30
lung	14
bone	17
soft tissue	15
CNS	1
No. of metastatic sites	
1	6
2	8
≥ 3	16

Results

Patient characteristics

Thirty patients with multiple liver metastases were entered into the study (details in Table 1). The median number of previous chemotherapies was 2.5. Most of the patients ($n = 22$) received an anthracycline and taxane prior to Mi-Fu-Fo. All patients with hormone-dependent disease received hormonal treatment. Approximately half of the patients (55%) had three or more involved organs. Two patients had liver metastases at the time of primary diagnosis. Seventeen patients had hyperbilirubinemia, four of whom had grade II, five grade III and eight grade IV hyperbilirubinemia. Thirteen patients had elevated liver enzymes as defined previously without hyperbilirubinemia.

Chemotherapy administration

In total, 109 cycles of chemotherapy were administered during the study. The median number of cycles per patient was 4 (range 1–9). The median cumulative dose of mitomycin C was 32 mg/m^2 (range 8–72 mg/m^2). All treatment cycles were administered as scheduled.

Toxicity

Twenty-three patients who completed the first cycle could be evaluated for toxicity. Seven patients died during the first cycle, 17 patients completed more than two cycles of Mi-Fu-Fo irrespective of the presence of jaundice and hyperbilirubinemia at the start of chemotherapy. Fourteen patients completed five or more cycles.

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Table 2 Hematologic toxicities according to the NCI-CTC criteria ($n=23$)

	Total	Grade III–IV
Leukocytopenia	16	9
Febrile leukocytopenia	2	2
Infection	2	1
Anemia	16	2
Thrombocytopenia	13	6

Table 3 Non-hematologic toxicities according to the NCI-CTC criteria ($n=23$)

	Total	Grade III–IV
Nausea	6	2
Mucositis	12	1
Diarrhea	3	3
Fatigue	16	9
Renal toxicity/HUS	0	1
Deep vein thrombosis	0	2

Table 4 Response rates and survival analysis ($n=30$)

	n	%
Best overall response		
CR	0	
PR	6	20
SD	12 ($\geq$ 6 months 8)	
PD	12 (<2 cycles 7)	
TTP (median)	4.5 months	
responders (median)	7.0 months	
Overall survival (median)	6.0 months	
responders (median)	12.0 months	

Hematological toxicity was the most frequent adverse event. Leukocytopenia grade III/IV developed in 30% of the patients and was associated with fever in two patients. One patient received secondary prophylactic granulocyte colony stimulating factor experiencing grade IV granulocytopenia. Thrombocytopenia grade III/IV occurred in six patients (20%). Grade III/IV anemia developed in only two patients (6.6%) with no need for transfusion (Table 2). Chemotherapy was stopped in two patients with grade IV hematological toxicity.

Mucositis and fatigue were the most common non-hematological toxicities (Table 3). One patient, who had received a cumulative dose of 48 mg/m^2 mitomycin developed renal failure due to HUS 6 months after treatment.

Results

Six patients (20%) achieved a partial remission (PR). Of the 12 patients with stable disease (SD), eight maintained SD for more than 6 months. Seven patients died after the first cycle due to disease progression (Table 4). The TTP of the whole study population was 4.5 months. However, patients who had a PR or SD for more than 6 months had a TTP of 7 months. The overall survival was 6.0 and 12.0 months, respectively (Table 4).

All patients with hyperbilirubinemia and elevated liver enzymes up to $6\times$ UNL received at least two cycles of chemotherapy. All patients ($n=8$) with elevated liver enzymes $\geq 10\times$ UNL had concomitant hyperbilirubinemia. Six of the eight patients, with combined hyperbilirubinemia, jaundice and elevated liver enzymes $\geq 10\times$ UNL, died within 2 weeks of the first cycle of chemotherapy. However, 25% (two of eight) of these patients survived 5 and 13 months, respectively. The overall survival was significantly longer for the patients without hyperbilirubinemia (Fig. 1).

Patients with a clinical benefit (PR + SD ≥ 6 months, $n=14$) had a significantly longer median overall survival (Fig. 2) than patients who did not benefit ($n=16$) (12.0 versus 1.5 months; log-rank $p<0.0001$). The characteristics of the patients who benefited are outlined in Table 5. Half of the patients with a clinical benefit (responding) and 11 of the non-responders had hyperbilirubinemia. The median numbers of previous chemotherapies was two in the responding and three in the non-responding group. The median age tended to be somewhat lower in the responding group (49 versus 55 years). Only one of the 10 patients with ascites achieved a clinical benefit.

Discussion

Patients with breast cancer metastasizing in the liver and causing liver dysfunction have a poor prognosis and limited therapeutic options [11]. Hepatic involvement in metastatic breast cancer can be associated with decreased drug-metabolizing ability, which can lead to an increase in toxicity or a decrease in the efficacy. Anthracyclines and taxanes are metabolized and excreted by the liver, and may cause severe side-effects in patients with impaired liver function [12–16]. It has been recently demonstrated by Sharma *et al.* in a pilot study in 11 patients that the combination of vinorelbine and cisplatin is able to normalize liver function in patients with metastatic breast cancer [17]. Although many cancer patients have liver metastases with abnormal liver biochemistry tests, there is no general accepted scheme to define liver dysfunction in patients with cancer. The Child–Pugh classification, based on serum albumin, bilirubin, prothrombin time, the degree of ascites and encephalopathia, is widely used in patients with cirrhosis [18]. Unfortunately it does not reflect the degree of liver dysfunction and the altered metabolism of cytotoxic drugs in cancer patients. We used a widely accepted definition of liver dysfunction in cancer patients. Liver enzymes $>3\times$ UNL or $1.5\times$ UNL associated with an elevated AP of $>2.5\times$ UNL were defined as liver

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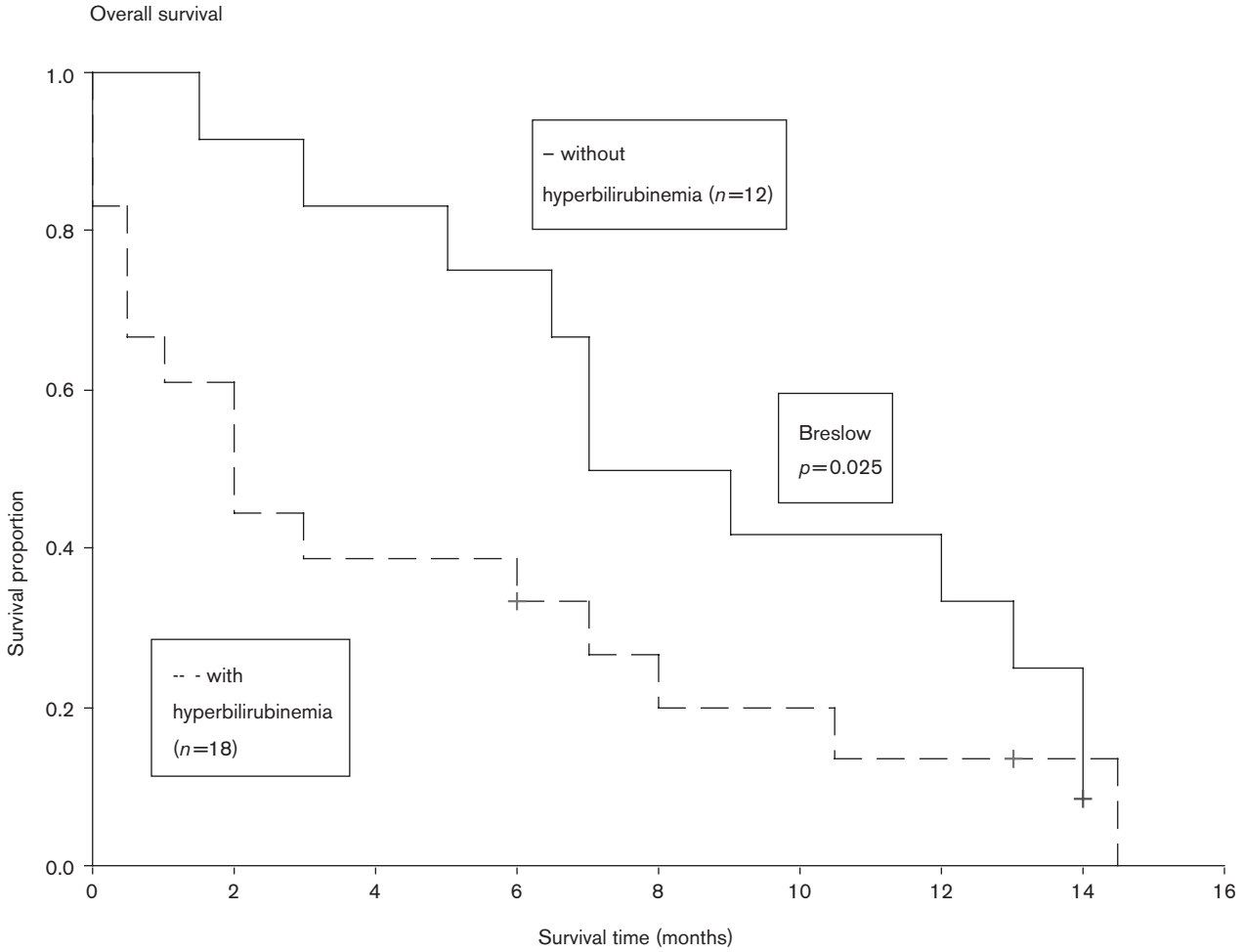
Fig. 1



Kaplan–Meier plot for the overall survival rate depending on the hyperbilirubinemia. Patients without hyperbilirubinemia (solid line; $n=12$) had a significant longer median overall survival than patients with hyperbilirubinemia (dashed line; $n=18$) (7.0 versus 2 months; log-rank $p=0.12$; Breslow $p=0.025$; Tarone–Ware $p=0.047$).

dysfunction. These tests are used to assess eligibility for clinical trials, are easily available in the daily routine and correlate with altered pharmacokinetics of several cytotoxic agents [14,19]. Another scoring system introduced by Twelves *et al.* [20] determines the effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. They demonstrated that there are no differences in the pharmacokinetics and the bio-activation of capecitabine.

Mitomycin C is a bio-reductive drug. It needs to be activated to toxic metabolites preferentially under hypoxic conditions [21]. It has been reported that the neuronal nitric oxide synthase (n-NOS), which is calcium dependent, is involved in catalyzing the reduction of mitomycin C under anaerobic conditions [22]. Moreover mitomycin C inhibits the inducible nitric oxide synthase (i-NOS), which can also be induced by hypoxia [23]. In the center of metastases there are usually hypoxic conditions. Therefore, mitomycin C might be an ideal drug for patients with either large metastases or rapidly growing metastases.

Despite their unfavorable prognosis we wanted to offer these patients a treatment option and started a phase II trial especially designed for patients with liver dysfunction. The combination chemotherapy was chosen, because of the promising response rates (36.6%), median duration of response (6 months) and median survival (10 months) after failing first- and second-line chemotherapy [9].

There seems to be a correlation between the extent of impaired liver function and the obtainable therapeutic

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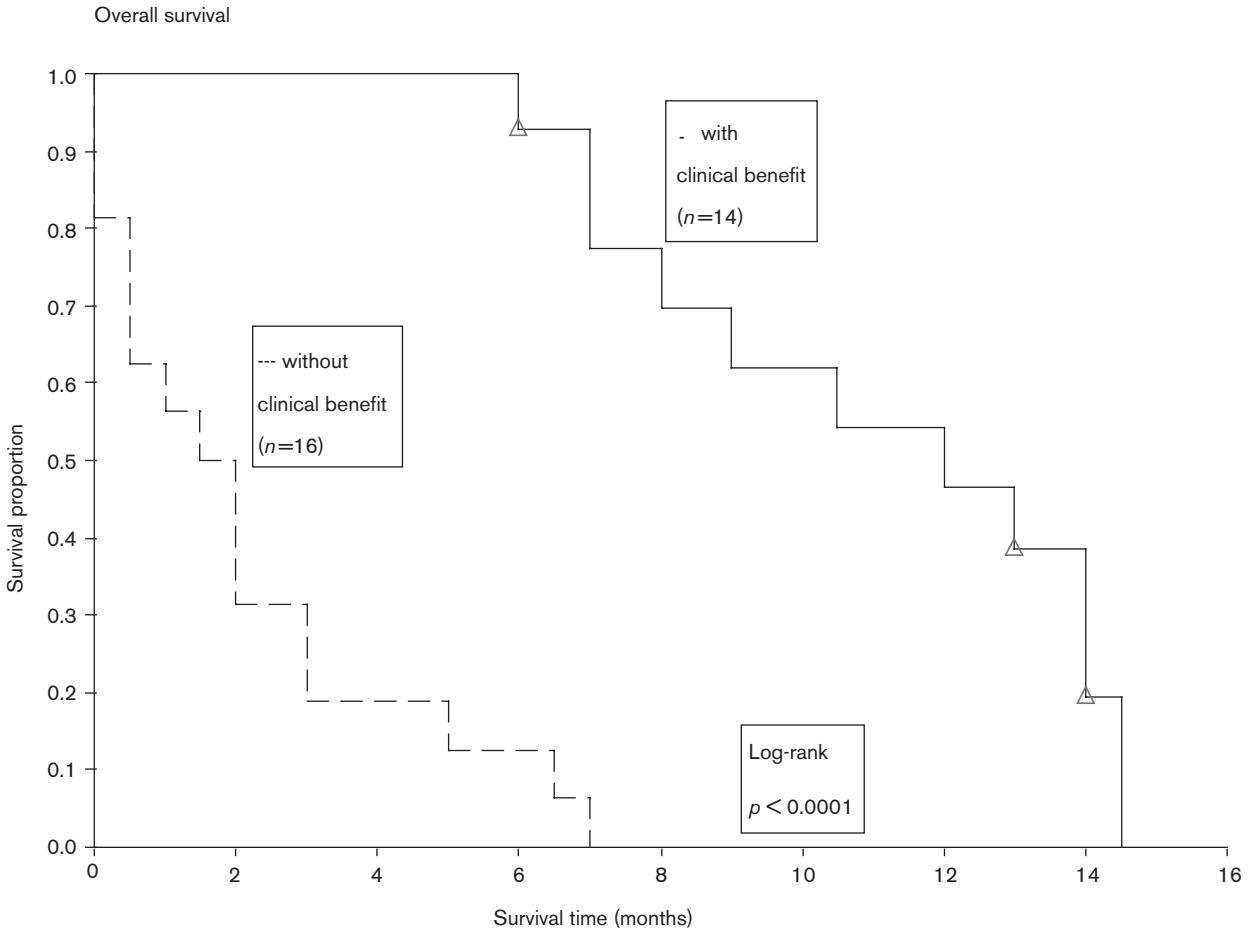
Fig. 2



Kaplan–Meier plot for the overall survival rate depending on the response. Patients with clinical benefit (solid line; $n=14$) had a significant longer median overall survival than patients who did not respond (dashed line; $n=16$) (12.0 versus 1.5 months; log rank $p<0.0001$).

Table 5 Characteristics of patients with clinical benefit (PR + SD $\geq$ 6 months; $n=14$)

Patient no.	Liver function[a]	No. of previous chemotherapies	Hormone-dependent disease	Time first diagnosis to Mi-Fu-Fo (months)
1	1	1	–	36
2	1	2	+	36
3	2[b]	0	+	30
4	2	3	–	NA
5	2	0	+	24
6	1	4	+	105
7	1	2	+	48
8	1	1	+	30
9	2	1	–	9
10	2	3	+	98
11	2	4	+	74
12	1	2	–	10
13	1	3	+	94
14	2	4	–	29

[a]Liver function: 1 = without hyperbilirubinemia; 2 = hyperbilirubinemia.
[b]Patient had ascites.

benefit. However, even patients with extremely high liver enzymes had a chance of responding to the therapy. The therapeutic effect could be related to ascites, but not to any other clinical factors like time from first diagnosis to start of Mi-Fu-Fo, median number of previous chemotherapies, median age and hormone-dependent disease. The response rates of Mi-Fu-Fo treatments do not differ from other third- and fourth-line therapies. The objective response rate is in line with earlier reports of the combination [24,25].

The toxicity of the combination is acceptable for patients with advanced disease. The high frequency of bone marrow toxicity is related to the pre-treatment. One patient developed a HUS 6 months after she stopped chemotherapy at a total dose of 48 mg/m^2 mitomycin C. Renal toxicity was seen in 2–5% of patients who had received less than 50 mg/m^2 mitomycin C [26].

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Conclusions

The risk–benefit analysis in these patients being treated with Mi-Fu-Fo appears to be positive as the natural life expectancy without treatment has to be considered to be very short. Up to 50% of the patients had a benefit from the treatment which corresponded to a time to the next tumor progression of 7.0 months and an overall survival of 12.0 months. However, patients with ascites did not seem to benefit from this therapy. Mi-Fu-Fo appears to provide a feasible and moderately toxic option to patients in this situation, where otherwise only limited treatment options were available until now.

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