Combined Chemotherapy with Mitomycin C, Folinic Acid, and 5-Fluorouracil (MiFoFU) as Salvage Treatment for Patients with Liver Metastases from Breast Cancer – a Retrospective Analysis

Michael H.R. Eichbaum^a Anne-Sybil Gast^a Thomas Bruckner^b Andreas Schneeweiss^a
Christof Sohn^a

^aDepartment of Gynecology and Obstetrics,

^bDepartment of Medical Biometry, University of Heidelberg Medical School, Germany

Key Words

Metastatic breast cancer · Liver metastases · Mitomycin · 5-Fluorouracil · Folinic acid

Summary

Background: The aim of this study was to analyze the activity and tolerability of a combined chemotherapy with mitomycin C, folinic acid, and 5-fluorouracil (MiFoFU) in patients with hepatic metastases from breast cancer, and in particular in patients with impaired liver function. **Patients and Methods:** We retrospectively studied the charts of 44 patients who were treated with a MiFoFU combination therapy because of progressive metastatic breast cancer. Predominant site of metastases was the liver. Primary endpoints were response and time to progression (TTP); secondary endpoints were overall survival (OS) and tolerability. **Results:** Median age prior to treatment was 59 years. A median of 6 treatment cycles were administered per patient. Clinical benefit rate amounted to 64%. A mean TTP of 9 months and a mean OS of 14 months were found. Main clinical signs of non-hematological toxicity were stomatitis, nausea, and diarrhea. Grade III/IV hematotoxicity was seen in only 9 patients. 16 patients showed clinical signs of liver dysfunction. A clinical benefit could be achieved in 8 of these patients. **Conclusions:** MiFoFU combination chemotherapy is a well-tolerated treatment alternative in the palliative therapy of patients with liver metastases from breast cancer. Particularly in patients with hepatic dysfunction, this regimen seems to represent a helpful treatment option.

Schlüsselwörter

Metastasiertes Mammakarzinom · Lebermetastasen · Mitomycin · 5-Fluorouracil · Folinat

Zusammenfassung

Hintergrund: Ziel dieser Studie war es, die Aktivität und Verträglichkeit einer Kombinationschemotherapie bestehend aus Mitomycin C, Folinat und 5-Fluorouracil (MiFoFU) in der Behandlung von Patientinnen mit Lebermetastasen eines Mammakarzinoms zu evaluieren. Insbesondere Patientinnen mit eingeschränkter Leberfunktion wurden untersucht. **Patientinnen und Methoden:** Wir analysierten retrospektiv die Krankenakten von 44 Patientinnen, die aufgrund eines progredienten metastasierten Mammakarzinoms mit einer MiFoFU-Kombinationschemotherapie behandelt wurden. Hauptmetastasenlokalisation war die Leber. Primäre Studienziele waren Therapieansprechen und Zeit zur Progression, sekundäre Studienziele waren Gesamtüberleben und Verträglichkeit. **Ergebnisse:** Das mediane Alter vor Behandlungsbeginn betrug 59 Jahre. Im Median wurden 6 Therapiezyklen pro Patientin verabreicht. Die Clinical-benefit-Rate lag bei 64%. Eine mittlere Zeit zur Progression von 9 Monaten und ein mittleres Gesamtüberleben von 14 Monaten wurden ermittelt. Wichtigste nichthämatologische Toxizitäten waren Stomatitis, Übelkeit und Diarrhoe. Grad III/IV-Hämatotoxizität wurde nur bei 9 Patientinnen beobachtet. 16 Patientinnen zeigten klinische Anzeichen einer Leberdysfunktion. Bei 8 dieser Patientinnen konnte ein klinischer Benefit erreicht werden. **Schlussfolgerungen:** Eine MiFoFU-Kombinationchemotherapie ist eine gut verträgliche Alternative in der palliativen Therapie von Patientinnen mit Lebermetastasen eines Mammakarzinoms. Insbesondere für Patientinnen mit eingeschränkter Leberfunktion scheint dieses Regime eine hilfreiche Option darzustellen.

Introduction

The occurrence of liver metastases represents a particular challenge for the systemic therapy of patients with metastatic breast cancer (MBC) [1–3]. Although long-term survival can be achieved in some patients with limited hepatic disease [4], the prognosis for patients with disseminated liver metastases is commonly poor, and a median survival of 14 months after initial diagnosis of liver metastases can be expected [5, 6]. Advanced liver metastases can cause hepatic dysfunction which is clinically apparent by hepatomegaly, jaundice, or the formation of ascites due to cholestasis and/or portal hypertension [7–9].

In general, liver metastases from breast cancer respond to chemotherapy [10], and anthracyclines and taxanes are still the most effective drugs for first-line treatment [11–12]. However, the efficacy of chemotherapy is frequently suboptimal as compared to other metastatic sites, as drug activity can be affected by impaired metabolic liver function [1]. Furthermore, hepatic dysfunction often limits the therapeutic options in these patients due to insufficient biliary drug clearing [8, 9], and severe toxicity has been reported after administering standard dose regimens [13–15]. In particular, persisting hyperbilirubinemia with serum levels > 2 mg/dl precludes the use of most cytotoxic drugs [16, 17]. In contrast to this, reports have also been published indicating that metastasis-induced hepatic dysfunction normalized after careful, effective cytotoxic treatment [18–21].

Mitomycin C (MMC) is active in the treatment of many solid tumors including breast cancer, with response rates of about 15–20% in pretreated breast cancer patients [22, 23]. Because of its unique efficacy in hypoxic tumor areas, MMC represents an interesting combination drug [24]. This is of particular interest in the treatment of patients suffering from hepatic metastases, as hypoxic areas have been found in the core of secondary liver tumors [25]. Therefore, MMC has been used as single-agent therapy in studies evaluating isolated hyperthermic liver perfusion in patients with advanced liver metastases [26]. The antimetabolite 5-fluorouracil (5-FU) is widely used in the adjuvant and palliative treatment of patients with breast cancer and can be combined with more myelotoxic drugs due to its moderate bone marrow toxicity [27, 28]. Furthermore, 5-FU combined with folinic acid has proven to be more active than 5-FU alone in treating many chemoresistant tumors, and is considered the ‘gold standard’ in the therapy of colorectal cancers [29–31]. Finally, capecitabine, an oral fluoropyrimidine that mimics continuous infusion of 5-FU, has also shown signs of being active in MBC patients with advanced liver metastases [20, 21]. Combination chemotherapies consisting of MMC and 5-FU have been shown to be effective in the palliative treatment of patients with advanced gastric or colorectal cancer [32–35]. In addition, MMC and 5-FU are active anti-neoplastic drugs that can be combined for the palliative therapy of MBC, even after intensive pretreatment [36–38]. More-

Table 1. Main patient characteristics (n = 44)

Age, years, median (range)	59 (24–76)
	Patients, n, median
Menopausal status	
Premenopausal	3
Postmenopausal	41
Histology of primary tumor	
Invasive ductal carcinoma	40
Invasive lobular carcinoma	3
Other	1
Grading	
G I	0
G II	18
G III	22
Data missing	4
Hormonal receptor status	
ER/PR-positive	32
ER/PR-negative	9
Data missing	3
Different metastatic sites, n	
1	13
2	20
3	11
WHO performance before start of MiFoFU	
0	22
1	20
≥ 2	2
Chemotherapy regimens in palliative setting, n	
0	11
1	25
≥ 2	8
Administered chemotherapy cycles, n	
Total	239
Per patient, median (range)	6 (3–10)

ER = Estrogen receptor; PR = progesterone receptor; MiFoFU = mitomycin C/folinic acid/5-fluorouracil.

over, a combination chemotherapy consisting of MMC, folinic acid, and 5-FU (MiFoFU) has been shown to be active and safe in the treatment of patients with advanced liver metastases secondary to breast cancer and hepatic dysfunction [39]. The aim of this retrospective analysis was to study the activity and tolerability of MiFoFU combination chemotherapy in a larger cohort of patients with liver metastases from breast cancer. In particular, patients in whom liver dysfunction was clinically apparent were studied.

Patients and Methods

Study Design and Patients

The charts of all patients with MBC who received MiFoFU combination chemotherapy at the University of Heidelberg Medical School, Department of Gynecology and Obstetrics, between 1998 and 2003 were studied. Patients had to be women, aged 18 years or over, with an ECOG performance status of 0–3. Liver metastases had to have been proven by clinical findings and imaging studies (ultrasound and/or computed tomogra-

Table 2. Response rates and survival data (entire study population, n = 44)

Complete remission, n (%)	2 (5)
Partial remission, n (%)	4 (9)
Stable disease, n (%)	23 (52)
Clinical benefit rate ^a , n (%)	28 (64)
Progressive disease, n (%)	15 (34)
Median time to progression, months	9 (range 2–40)
Median overall survival, months	14 (range 1.5–91)

^aComplete + partial response + stable disease $\geq$ 6 months.

Table 3. Non-hematological toxicity

Toxicity	Grade I, n (%)	Grade II, n (%)	Grade III, n (%)	Grade IV, n (%)
Non-hematological				
Stomatitis	10 (23.8)	0 (0)	0 (0)	1 (2.3)
Nausea/vomiting	10 (23.8)	1 (2.4)	1 (2.4)	0 (0)
Diarrhea	17 (40.5)	0 (0)	0 (0)	0 (0)
Hematological				
Anemia	16 (38.1)	16 (38.1)	1 (2.4)	0 (0)
Leukopenia	8 (19.5)	9 (22)	5 (12.2)	1 (2.44)
Thrombocytopenia	8 (19)	6 (14.3)	5 (11.9)	0 (0)

phy/magnetic resonance imaging). All analyses were performed according to the Declaration of Helsinki.

Treatment Schedule

All patients received a 4-week treatment schedule of MMC (8 mg/m², 15-min intravenous (i.v.) infusion) on day 1, and folinic acid (500 mg total dose, i.v. bolus) plus 5-FU (750 mg/m², 2-h i.v. infusion) on days 1 and 2. Prednisone 50 mg was administered orally from day 1 to 5 to prevent pulmonary toxicity. Dexamethasone 8 mg i.v., ondansetron 8 mg i.v., and ranitidine 50 mg i.v. were added on days 1 and 2 to prevent nausea and gastrointestinal toxicity. Toxicity was assessed before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Cellular blood cell counts were taken weekly, or more often if clinically indicated. Blood chemistry values were checked before each treatment cycle.

Study Endpoints

Primary endpoints were response rate and time to progression (TTP); secondary endpoints were overall survival (OS) and tolerability. Complete remission (CR) was defined as complete disappearance of all clinical, radiographic, and biochemical evidence of disease. Partial remission (PR) meant a 50% or greater reduction of the sum of the product of the longest diameter and its perpendicular of all measurable lesions. Progressive disease (PD) was defined as the appearance of new lesions, significant increase in tumor markers (>50%), or radiographic increase of $\geq$ 25% in the sum of the products of the longest diameter and its perpendicular, as compared with the lowest value recorded. Patients without CR, PR, or PD were considered as having stable disease (SD). The clinical benefit rate (CBR) was determined as rate of patients with either CR or PR or with SD for more than 6 months. TTP was calculated from the start of treatment until progression occurred. OS was determined as the time interval between commencement of therapy and death of the patient or date of the last observation. Toxicity and tolerability analyses were per-

Table 4. Characteristics of patients with clinical signs of reduced or impaired liver function (n = 16)

Age, years, median (range)	61 (40–76)
WHO performance status before start of MiFoFU	
0	4
1	9
$\geq$ 2	2
Number of different metastatic sites	
1	5
2	6
$\geq$ 3	5
Different chemotherapy regimens in palliative setting, n	
0	3
1	9
$\geq$ 2	4
Jaundice	5
Hepatomegaly	7
Ascites	4
ASAT, U/l, median (range)	78 (12–678)
ALAT, U/l, median (range)	46 (6–140)
GGT, U/l, median (range)	170 (34–409)
AP, U/l, median (range)	370 (79–1,317)
Bilirubin, mg/dl, median	1.8 (0.3–8.4)

MiFoFU = Mitomycin C/folinic acid/5-fluorouracil; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; GGT = γ -glutamyltransferase; AP = alkaline phosphatase.

formed in all patients who completed at least 1 cycle of therapy. Hematological and non-hematological toxicities were evaluated and graded according to the NCI-CTC.

Results

Patient Characteristics

In all, 44 patients were eligible for retrospective analysis. Median age was 59 years (range 24–76). In 13 patients, the liver was the only proven site of metastasis; 11 patients suffered from metastatic disease involving 3 or more different sites. In terms of pretreatment, 33 patients had already received at least 1 palliative chemotherapy regimen, and 11 patients had been treated with MiFoFU as first-line therapy for MBC. Including adjuvant therapies, a total of 35 patients (81%) had received anthracycline pretreatment upon entry in the study, 11 patients (25%) had previously received taxanes, and 9 patients were refractory to treatment with anthracyclines and taxanes (20%). The median number of chemotherapy cycles administered per patient was 6 (range 3–10), with a total number of 239 cycles. At the time of the analysis, 44 patients had died as a result of disease progression. Table 1 provides further details about the main patient characteristics.

Table 5. Subgroup analysis: activity and tolerability in patients with hepatic dysfunction

Survival data, months, median (range)	
Time to progression	6.5
Overall survival	8.6
	Patients, n, median (range)
Response	
Complete remission	0 (0)
Partial remission	1 (6)
No change	7 (44)
Clinical benefit rate ^a	8 (50)
Progressive disease	8 (50)
Non-hematological toxicity	
Stomatitis (grade III/IV)	0 (0)
Nausea/vomiting (grade III/IV)	0 (0)
Diarrhea (grade III/IV)	0 (0)
Hematological toxicity	
Anemia (grade III/IV)	0 (0)
Leukopenia (grade III/IV)	2 (13)
Thrombocytopenia (grade III/IV)	6 (38)

^aComplete + partial response + stable disease $\geq$ 6 months.

Fig. 1. Kaplan-Meier analysis of time to progression (TTP; months), stratified according to presence or absence of signs of liver dysfunction ($p < 0.05$).

Fig. 2. Kaplan-Meier analysis of overall survival (OS; months), stratified according to presence or absence of signs of liver dysfunction ($p = 0.08$).

Response Rates and Survival Analysis

Two patients (5%) showed a CR, and 4 patients (9%) a PR, with an overall response rate (ORR) of 14%. In 23 patients (52%), SD was achieved. Due to the fact that response could only be measured according to our defined criteria in a minority of the patients, some patients were classified as having SD although their clinical response to treatment was excellent. In summary, the CBR (CR + PR + SD $\geq$ 6 months) amounted to 64%. In 15 patients (34%), disease progressed. Median TTP and median OS were 9 and 14.3 months, respectively (table 2).

Toxicity

In general, the treatment was well tolerated. No therapy-related deaths occurred. The most frequent adverse event was leukopenia, as grade III/IV in 6 patients (15%). No febrile neutropenia was observed. Five patients (12%) developed grade III/IV thrombocytopenia, and in 1 patient (2%) a grade III anemia was found. In summary, grade III/IV hematotoxicity was seen in 9 patients (20%). In terms of non-hematological toxicity, diarrhea, stomatitis, and nausea were reported most often. Most toxic reactions were mild, consistent with a grade I/II toxicity. One patient (2.3%) showed a grade III stomatitis, another patient grade III nausea/vomiting. Table 3 provides an overview of the documented toxicities in the study population. Due to adverse events, the dose had to be reduced and treatment delayed in 7 and 6 patients, respectively. In 6 patients, treatment had to be discontinued due to intolerable toxicity.

Patients with Reduced or Impaired Liver Function

A total of 16 patients showed signs of reduced or impaired liver function. Reduced liver function was clinically defined as the presence of hepatomegaly, jaundice, or formation of ascites. Furthermore, according to previously published criteria [39], patients in whom serum levels of liver enzymes (alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), γ -glutamyltransferase (GGT)) were elevated above 3 times the upper normal limit (≥ 3 UNL) or ≥ 1.5 UNL plus alkaline phosphatase (AP) ≥ 1.5 UNL were also included in this group. Table 4 provides an overview of the main patient characteristics. The median number of administered treatment cycles was 5 (range 3–9). Eight patients (50%) showed a clinical benefit (1 PR, 7 SD), and in 8 patients (50%) disease progressed during chemotherapy. The median TTP and OS were 6.5 months and 8.6 months, respectively (table 5, figs. 1, 2). Non-hematological toxicity was mild and only occurred in 6 patients, consistent with grade I/II toxicity. No grade III/IV anemia was observed within this subgroup, 2 patients developed grade III/IV leukopenia (13%), and 6 patients grade III/IV thrombocytopenia (38%).

Discussion

The treatment of liver metastases from breast cancer represents a particular challenge in the management of MBC patients. Hepatic metastases can cause liver dysfunction associated with increased toxicity and limited antineoplastic activity of the administered chemotherapeutics. Although anthracyclines and taxanes are still the preferred drugs for first-line treatment [10–12], we demonstrated that the MiFoFU combination chemotherapy regimen consisting of MMC, folinic acid, and 5-FU represents an active salvage therapy in patients with predominant liver metastases. The clinical benefit rate of 64% was satisfactory even in patients who had previously received

anthracycline and taxane pretreatment. MiFoFU could be managed well in an outpatient setting. Only 6 patients (14%) discontinued the treatment due to adverse events. Furthermore, with the 4-week schedule, patients only need to visit the hospital twice a month. Finally, this regimen can be administered at relatively low costs.

Liver metastases may cause hyperbilirubinemia either as a result of obstructive cholestasis [9] or disseminated intrahepatic spread and damage to the liver parenchyma [40]. Most cytotoxic drugs cannot be delivered at standard dosages under these circumstances [16, 17], and severe toxicity has been observed [13–15]. Nevertheless, promising reports have been published on the successful treatment of MBC patients with advanced liver metastases and associated normalization of an initially reduced liver function [18–21]. Accordingly, it is important to search for alternative strategies for treating patients with hepatic dysfunction, i.e. hyperbilirubinemia, due to breast cancer liver metastases. We previously reported on the management of such a patient who presented with hyperbilirubinemia of 20 mg/dl and was successfully treated after endoscopic stenting of the common bile duct and subsequent salvage chemotherapy with MiFoFU in increasing doses [9]. Moreover, Loibl et al. [39] recently showed that a combined MiFoFU chemotherapy was feasible and active in a series of 30 MBC patients with hepatic dysfunction due to advanced liver metastases [39]. Our results are in line with these data, although our survival data were slightly better for a comparable subgroup. This might be explained by the fact that only 5 patients with hyperbilirubinemia were included in our study, whereas Loibl et al. [39] reported on 18 such patients.

Toxicity was generally acceptable, mainly as hematotoxicity.

We observed grade III/IV thrombocytopenia and leukopenia in 20% of all studied patients. Patients with hepatic dysfunction presented more often with grade III/IV thrombocytopenia (38 vs. 12% in all), whereas all other toxicity remained similar. Thus, a careful monitoring of the cellular blood cell count provided, these data suggest that salvage therapy with MiFoFU is equally feasible, independent of adequate hepatic clearing function.

The question whether to use a single agent or combination therapies in patients with MBC, is still not answered and should be decided on an individual basis [41, 42]. As we previously reported, MiFoFU combination chemotherapy appears to be ideal in clinical settings where faster remission is needed and the risk of major toxicities should be avoided [38]. This is frequently the case in patients with breast cancer-derived liver metastases. Thus, MiFoFU can be considered as an alternative beside monotherapies, mainly used in settings without urgent need for remission, and more toxic combination therapies, preferred for symptomatic patients in whom a fast symptom relief is needed.

In summary, MiFoFU combination therapy appears to be a reasonable and well tolerated alternative as salvage treatment for patients with liver metastases from breast cancer. This regimen is also active and feasible in patients showing clinical signs of reduced or impaired hepatic function. As our study is limited by its retrospective attempt, future clinical trials with a prospective design are warranted to confirm this hypothesis, especially for patients with hepatic dysfunction. This strategy may offer an important option for MBC patients with weak performance and in whom treatment is limited due to hepatic metastases.

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