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CLINICAL TRIAL

Intra-arterial Mitomycin C infusion in a large cohort of advanced liver metastatic breast cancer patients: safety, efficacy and factors influencing survival

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Abstract

Purpose The aim of this study was to determine the safety and efficacy of Mitomycin C (MMC) infusion in a large cohort of advanced liver metastatic breast cancer patients (LMBC) and to determine factors influencing overall survival (OS).

Methods We retrospectively analysed LMBC patients, treated with MMC infusion between 2000 and 2017. Hepatic response was measured with baseline CT scans and first available CT scan after MMC infusion by RECIST 1.1 criteria. Adverse events were registered by the CTCAE version 5.0. OS and hepatic progression free survival (hPFS) were evaluated using Kaplan–Meier estimates. After univariable analysis, a stepwise forward multivariable (MV) prediction analysis was developed to select independent pre-treatment factors associated with OS.

Results We included 176 patients with a total of 599 MMC infusions, mostly heavily pre-treated patients with a median time from diagnosis of MBC to MMC infusion of 36.9 months. RECIST evaluation of liver lesions ($n = 132$) showed a partial response rate of 15%, stable disease of 43% and progressive disease in 17%. Adverse events grade 3 and 4 were reported in 17.5%. Median PFS was 5.5 months and median OS was 7.8 months. Significant independent baseline predictors of worse OS included number of prior systemic chemotherapy lines, prior liver ablation, higher liver tumour burden and elevated levels of bilirubin and ALT.

Conclusion MMC infusion is safe and effective in advanced LMBC patients. An increased number of prior therapies, a higher liver tumour burden and elevated levels of bilirubin and ALT were associated with a worse OS.

Keywords Metastatic breast cancer · Liver metastases · Chemo resistant · Intra-arterial therapy · Mitomycin C infusion

Abbreviations

MBC	Metastatic breast cancer
LMBC	Liver metastatic breast cancer
MMC	Mitomycin C
HUS	Haemolytic uremic syndrome
CT	Computed tomography
RECIST	Response evaluation criteria in solid tumours
PR	Partial response
CR	Complete response
SD	Stable disease
PD	Progressive disease
CTCAE	Common terminology criteria for adverse events
hPFS	Hepatic progression free survival
OS	Overall survival
HR	Hazard ratio
CI	Confidence interval

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ALT Alanine transaminase
NR No response assessment

Introduction

Breast cancer is the world leading type of cancer in women [1]. Localized breast cancer has a 5 year survival rate around 99% [2]. However, about 20–30% of women with breast cancer develop metastases at some point, which dramatically worsens the prognosis with a 5-year survival rate of 25% (all metastatic sites included) [3]. Liver metastatic breast cancer (LMBC) eventually occurs in 50% of metastatic breast cancer patients and is associated with worse prognosis of only a few years [4, 5]. In most cases the initial therapy for LMBC is systemic treatment by means of chemotherapy with taxanes or anthracyclines [6]. The efficacy and safety of the systemic chemotherapy can be affected by the hepatic dysfunction caused by the metastases which is therefore often a dose limiting factor [7, 8]. Local intra-arterial therapies can offer higher local concentration of chemotherapy to the liver metastases with less systemic effect due to the arterial blood supply of the metastases [9, 10]. Mitomycin C (MMC) is a classical chemotherapeutic agent that was originally used as an intravenously administered chemotherapeutic agent for systemic treatment of breast cancer [11]. Due to some rare, but severe systemic toxicities like the haemolytic uremic syndrome (HUS), and new upcoming other chemotherapeutics like anthracyclines and taxanes, the use of systemic intravenously administered Mitomycin C has significantly declined in the last decades [12, 13]. However, when MMC is locally infused in the hepatic arteries, a high first pass is obtained to the metastases with minimal effects to the healthy parenchyma. The low systemic toxicity of MMC may provide a break from systemic chemotherapy to recover from the toxicities. Maes et al. showed the safety of intra-arterial administration of MMC without major complications in a small cohort [14]. The purpose of this study was to evaluate a large cohort of LMBC patients treated with intra-arterial infusion of MMC in order to determine safety and efficacy of the treatment and to determine pre-treatment factors associated with overall survival (OS).

Methods

Study design

This study was approved by the ethics committee of our institute (S60596). The requirement for an informed consent was waived, due to its retrospective nature. Patients with liver metastatic breast cancer treated with intra-arterial MMC infusion between October 2000 and December 2017 were included. All breast cancer patients were prospectively registered in a follow-up database. This database plus patients records were retrospectively reviewed. Clinical results were analysed to obtain patients oncological history. All patients underwent baseline assessment of liver function, general blood count and coagulation factors at every cycle of MMC. Tumour burden was accessed by eyeballing of the total volume of tumour in the liver and was categorized as 0–25%, 25–50%, > 50%.

Mitomycin C infusion

Details of the MMC infusion procedure have been previously described [14]. The treatment was performed by, or supervised by, an expert interventional radiologist. Under local anaesthesia, femoral access was generally obtained in the right common femoral artery and a 4-French sheath was introduced. A micro catheter was used through a diagnostic 4-French catheter for selective catheterization of the right and left hepatic artery. A starting total of 12 mg Mitomycin C (MMC) in a 10 cc saline solution was administered divided over both liver lobes according to the liver volume. Subsequent dosing was done every 4 weeks or longer and the dose of Mitomycin C could be adjusted by physicians according to clinical performance and laboratory results.

Follow-up and response assessment

Treatment was evaluated by the first available computed tomography (CT) scan after MMC infusion. We measured hepatic response by comparing the liver CT before and after MMC infusing according to the response evaluation criteria in solid tumours (RECIST) criteria 1.1 with four categories [partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD)] [15]. Two hepatic target lesions were selected for the response in the liver.

The treating physician decided to continue MMC cycles based on radiological and biochemical results and patient performance. The maximum amount of MMC cycles was, in principle, 6 cycles (because of increased subsequent risk of HUS at higher cumulative dose); however additional MMC infusions could be considered in case of disease control without side effects. Administration of MMC cycles was stopped in patients with progressive hepatic or extra hepatic disease or due to unstable clinical or biochemical characteristics. Adverse events were registered by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by retrospective use of patient records and laboratory results.

Survival time was calculated from the date of first MMC cycle until death or loss to follow-up. Hepatic progression free survival (hPFS) was calculated from the first MMC cycle until hepatic progression on radiological images occurred.

Statistics

Pre-treatment patient and tumour characteristics are described as median and range for continuous variables and as frequencies and percentages for categorical variables. OS and hPFS were estimated using the Kaplan–Meier method starting at the date of the first cycle of MMC.

Cox proportional hazards models were used to analyse the prognostic effect of the pre-treatment characteristics on OS. Results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). Non-linear (quadratic) trends are tested for all continuous predictors. A forward stepwise model selection procedure was applied to develop a multivariable model for independent prognostic factors associated with OS. To specify, a significance level of 5% was used for both entry and removal of variables: step by step individual variables were added to the model, selecting in each step the variable leading to the lowest *p*-value and adding variables as long as the variable showed a significant *p*-value. Additionally, previously included variables turning non-significant along the procedure are removed from the model. All analyses are two-sided and a 5% significance level is assumed for all tests. Analyses were performed using SAS software (version 9.4 of the SAS System for Windows) and Statistical Package for the Social Sciences (SPSS, version 25, Chicago, IL).

Results

Patient characteristics

Table 1 shows the pre-treatment factors of the 176 patients treated with MMC between 2000 and 2017. Most patients had a ductal adenocarcinoma (84%) with a positive oestrogen receptor (80%), a positive progesterone receptor (66%) and a negative Her2 status (81%). Disease was mostly metastasized in a metachronous manner (82%). The tumour burden of the liver was greater than 25% in 85 (50% of the) patients. 73% of the patients had one or more extra hepatic sides of metastases (bone $n=98$, lung $n=31$, non-loco regional nodes $n=29$, abdominal $n=15$, pleura $n=6$, cutaneous $n=5$, mediastinal $n=5$, adrenal $n=4$, peritoneal $n=4$, brain $n=4$). At inclusion, patients had received a median of 4 systemic chemotherapeutic lines (range 0–11) in the metastatic setting before MMC infusion. We included only systemic chemotherapies in the metastatic setting without hormonal, HER2 therapies or chemotherapies in the adjuvant or neoadjuvant setting. Median time from diagnosis of metastatic disease until MMC infusion was 36.9 months (SD 35.6).

Treatment characteristics

Table 2 shows treatment factors of the MMC infusions. A total of 599 MMC cycles were given in 176 patients. The median age at first MMC infusion was 56 years (range 26–86). No patients received additional chemotherapy during MMC infusion. Nine patients underwent a hepatic resection and 3 patients a percutaneous thermal ablation for their hepatic disease before MMC infusion. After MMC infusion was stopped for any reason (in most cases progression), 50% of the patients received further systemic treatment with other chemotherapies, and 9 (5%) patients received local hepatic treatment consisting of intra-arterial radioembolization with yttrium 90 ($n=5$), external beam radiotherapy ($n=1$), percutaneous thermal ablation ($n=1$) and surgery ($n=2$).

Adverse events

In Table 3, all clinical and biochemical adverse events in 176 patients with a total of 599 MMC infusions are listed. Thrombocytopenia was the most often occurring adverse event. No grade 5 adverse events occurred after MMC infusion. Two patients developed an adverse event concerning the kidney. The first patient developed chronic kidney failure after the sixth cycle of MMC. This patient had a mono kidney and ended with permanent peritoneal dialysis (grade 4). The second patient developed a thrombotic microangiopathy after the sixth cycle of MMC which was treated with steroids (grade 2). A second grade 4 adverse event occurred and consisted of a thrombocytopenia below 25×10**9/L which was treated by 2 packages of platelets. The fact that methyl prednisolone was also prescribe could have contributed to the thrombocytopenia.

A sepsis was seen in one patient after the second MMC infusion that was treated with systemic antibiotic treatment. One patient developed an acalculous cholecystitis that was treated with laparoscopic cholecystectomy. Eight patients experienced a haematoma at the puncture site. An allergic reaction to the contrast agent appeared in 5 patients during the procedure, of which one had to be treated with intravenous medication (grade 3).

Response by RECIST

Post procedural CT for response assessment was available in 132 (75%) of the patients. Median time to RECIST response assessment was after 2 cycles of MMC infusion (range 1-5). Response rate in the liver after MMC consisted of PR ($n=26$, 14.8%) (Fig. 1), SD ($n=76$, 43.2%) and PD ($n=30$, 17%). In 44 patients (25%) no response assessment was obtained.

Table 1 Patient pre-treatment characteristics, and univariate analysis for overall survival

	$N = 176$	Univariate analysis	
		HR (95% CI)	*p*-Value
Aetiology primary tumour			0.39
Ductal	142 (84%)		
Lobular	21 (12%)		
Other	7 (4%)		
Hormone status primary tumour			
Positive oestrogen receptor	135 (80%)	0.9 (0.6;1.3)	0.58
Positive progesterone receptor	111 (66%)	0.96 (0.7;1.3)	0.81
Positive HER2 receptor	29 (19%)	1.1 (0.7;1.6)	0.75
Triple negative receptor status	18 (11%)	1.7 (1.0;2.7)	0.046
Diagnosis of liver metastasis			
Synchronous	32 (18%)	Ref	Ref
Metachronous	144 (82%)	0.8 (0.6;1.2)	0.33
Time from diagnosis of breast cancer to liver metastases, months	36.6 (0–329.5)	1.0 (0.99;1.00)	0.80
Liver tumour burden			< 0.0001
< 25%	85 (50%)	Ref	Ref
25–50%	44 (26%)	2.1 (1.5;3.1)	< 0.0001
> 50%	41 (24%)	2.9 (2.0;4.4)	< 0.0001
Extra hepatic sites of metastases			
Yes	129 (73%)	1.3 (0.9;1.8)	0.18
No	47 (27%)	Ref	Ref
Median systemic chemotherapy lines for MBC before MMC	4 (0–11)	1.1 (1.1;1.2)	< 0.0001
Prior hepatic treatment			
Surgery	9 (5%)	0.5 (0.2;0.97)	0.042
Ablation	3 (1.7%)	5.1 (1.6;16)	0.0058
Alanine aminotransferase level			
Normal < 31 µL	58 (34%)	Ref	Ref
Elevated > 31 µL	115 (66%)	1.9 (1.4;2.7)	0.0001
Bilirubin level total			
Normal < 1.18 mg/dL	153 (88%)	Ref	Ref
Elevated > 1.18 mg/dL	21 (12%)	2.98 (1.9;4.8)	< 0.0001
Haemoglobin			
Normal > 12–16 g/dL	86 (49%)	Ref	Ref
Declined < 12 g/dL	89 (51%)	1.3 (0.95;1.8)	0.098
White blood count			
Normal > 4.5*10**9/L	138 (89%)	Ref	Ref
Declined < 4.5*10**9/L	37 (21%)	0.8 (0.6;1.2)	0.37
Platelet count			
Normal > 100*10**9/L	169 (97%)	Ref	Ref
Declined < 100*10**9/L	6 (3%)	2.0 (0.9;4.6)	0.098
Kidney function (eGFR)			
Normal > 60 mL/min	128 (97%)	Ref	Ref
Declined < 60 mL/min	4 (3%)	0.6 (0.2;1.7)	0.36

Survival analysis

At time of analysis 3 patients were still alive; the other 173 patients had died. Median OS was 7.8 months (95% CI of 6.1–9.8). In Fig. 2 an overview is shown of the OS outlined in different groups (disease control (PR + SD), progressive disease (PD), no response assessment (NR)), a global test showed a significant difference between the three groups

Table 2 Treatment characteristics and response

Median age at first MMC infusion (years)	56 (26–86)
Median number of MMC cycles per patient	3 (1–11)
Median dose of MMC (mg)	12 (6–12)
Median number of cycles before response assessment	2 (1–5)
Response after MMC ($n=132$)	
Partial response	26 (14.8%)
Stabile disease	76 (43.2%)
Progressive disease	30 (17%)
No response assessment possible	44 (25%)

($p<0.0001$). Median survival for patients that obtained disease control was 11.9 months (CI 10–16.1) and 4.2 months (CI 2.8–6.9) for patients that showed PD ($p<0.0001$). In patients where no response assessment (NR) was not obtained, median survival was 1.7 months (1.3–2.4 months). Median hPFS in the 107 patients in which radiological follow-up was available was 5.5 months (CI 4.5–6.8) as shown in Fig. 3.

Factors influencing overall survival

Univariable analysis of the association of pre-treatment characteristics with overall survival is presented in Table 1. Multivariable analysis (Table 4) showed that a higher number of previous lines of systemic chemotherapy (HR = 1.2; CI 1.1–1.3), a higher tumour burden (> 50%) (HR = 2.4; CI 1.5–3.7), prior ablation of the liver (HR = 5.9; CI 1.8–19.4) and elevated levels of bilirubin (HR = 2.18; CI 1.3–3.8) and alanine transaminase (ALT) (HR = 1.5; CI 1.01–2.09) were independently associated with a worse OS. After the addition of response assessment by RECIST to the previously chosen multivariable model, PD by RECIST was significantly associated with a worse OS (PD vs. PR; HR = 3.98 CI 2.3–7.02, $p<0.0001$).

Discussion

In this study we demonstrated that MMC infusion was safe and effective in a cohort of 176 heavily pre-treated LMBC patients with a total of 599 MMC infusions. Multivariable analysis showed that an increased number of prior systemic chemotherapeutic lines, a higher tumour burden of the liver, prior ablation of the liver and elevated baseline levels of bilirubin and ALT, were independently associated with a worse OS.

Progression or resistance to systemic chemotherapy often occurs in the LMBC patients, which is associated with a worse survival [16]. To overcome this resistance, local intra-arterial therapies may offer high local concentrations of chemotherapy in the liver with low toxicity

Table 3 Adverse events after MMC infusion

Adverse events ($n=176$)	Grade 1	Grade 2	Grade 3	Grade 4
Clinical *n* (%)				
Fatigue	55 (31%)	4 (2%)	0	0
Pain	62 (35%)	2 (1%)	3 (2%)	0
Nausea	54 (31%)	2 (1%)	1 (0.5%)	0
Emesis	15 (8%)	0	0	0
Weight loss	8 (5%)	2 (1%)	0	0
Gastrointestinal ulcer	0	1 (0.5%)	0	0
Allergic reaction	3 (2%)	2 (1%)	1 (0.5%)	0
Hematoma at injection site	7 (4%)	1 (0.5%)	0	0
Sepsis	0	0	1 (0.5%)	0
Kidney disease	0	2 (1%)	0	1 (0.5%)
Other	35 (20%)	2 (1%)	1 (0.5%)	0
Biochemical *n* (%)				
Leukopenia	53 (30%)	12 (7%)	2 (1%)	0
Thrombocytopenia	96 (55%)	22 (13%)	6 (3%)	1 (0.5%)
Anaemia	43 (24%)	10 (6%)	0	0
Increased aspartate aminotransferase	30 (17%)	7 (4%)	3 (2%)	0
Increased alanine aminotransferase	24 (14%)	4 (2%)	1 (0.5%)	0
Increased bilirubin	8 (5%)	6 (3%)	8 (5%)	0
Increased alkaline phosphatase	11 (6%)	4 (2%)	1 (0.5%)	0
Increased gamma-glut amyl transferase	22 (13%)	3 (2%)	1 (0.5%)	0
Decrease in estimated glomerular filtration rate	5 (3%)	0	0	0

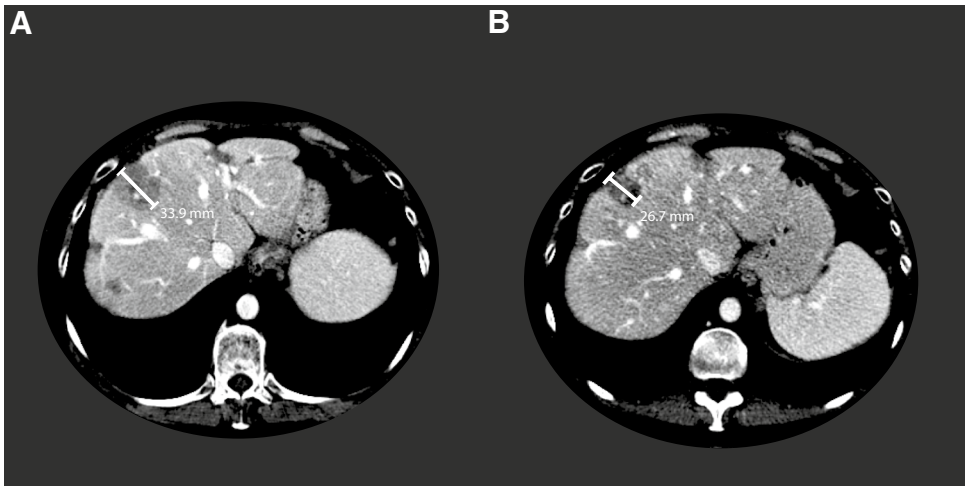

Fig. 1 Hepatic response before (**a**) and after (**b**) 2 cycles of MMC

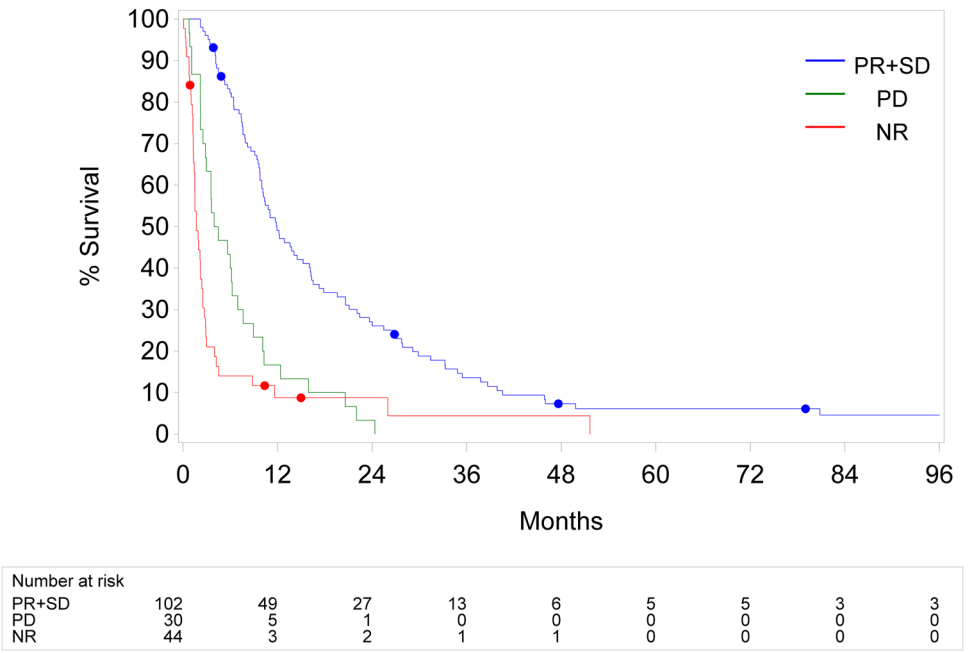

Fig. 2 Kaplan Meier curve overall survival by three groups; responders (PR + SD); non-responders (PD) and patients with no response assessment (NR). Median OS was 11.9 months for the responders, 4.2 months for the non-responders and 1.7 months for the patients with no response assessment

providing a break from systemic chemotherapy [10, 17]. Literature about MMC infusion in LMBC patients is very limited. Prior research demonstrated the safety of MMC in a smaller cohort of 30 patients [14]. In the present study of a large cohort, we confirmed that intra-arterial MMC infusion was safe with only 17.5% patients with a grade 3 or higher adverse events despite a heavily pre-treated metastatic breast cancer (MBC) population. These toxicity levels are low compared to other therapies for resistant metastatic breast cancer patients, such as Eribulin that has a 30% grade 4 adverse event and overall 99% adverse events [18, 19]. Ideally, intra-arterial MMC should be tested in a randomized phase III study compared to systemic therapy of physician's choice, but it is unlikely that such a study will ever happen.

A known severe systemic side effect of MMC administration is HUS [12, 13]. In the present study two patients had a side effect concerning the kidney; however, no HUS occurred in a total of 599 intra-arterial MMC infusions. Therefore we conclude that MMC can be safely used by intra-arterial infusion.

In this study we observed a median OS of 7.8 months. In the literature, other groups have reported a median OS of 7 months [20], 14 months [21], 13.2 months [22], 11.4 months [23] after MMC infusion [20], MMC with Folic acid plus 5-Fluorouracil [21], and MMC plus Gemcitabine [22, 23], respectively. These differences can be explained by the differences in disease extension and amount of prior therapy received before intra-arterial infusion. The rather low OS rate in our cohort certainly reflects the advanced

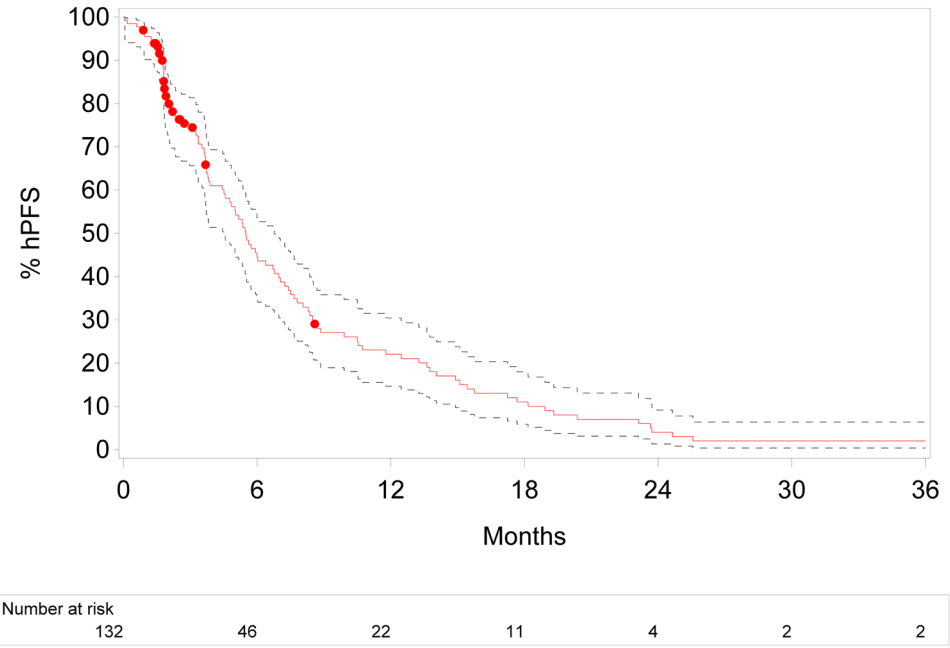

Fig. 3 Kaplan Meier curve of hepatic progression free survival (hPFS) by RECIST. Median hPFS was 5.5 months

Table 4 Multivariable model of factors influencing overall survival

Variable	Test	*N* (%)	Hazard ratio (95% CI)	*p*-Value
Systemic chemotherapy lines before MMC	Linear trend: + 1 unit	166 (95%)	1.166 (1.080; 1.259)	< 0.0001
Prior liver ablation	None	173 (98%)	Ref	Ref
	Performed	3 (2%)	5.938 (1.818; 19.395)	0.0032
Tumour burden liver	Global test			< 0.0001
	< 25%	85 (50%)	Ref	Ref
	25–50%	44 (26%)	2.050 (1.391; 3.022)	0.0003
	> 50%	41 (24%)	2.384 (1.534; 3.706)	0.0001
Baseline bilirubin level	Not elevated	153 (88%)	Ref	Ref
	Elevated	21 (12%)	2.183 (1.265; 3.767)	0.0050
Baseline ALT level	Not elevated	58 (34%)	Ref	Ref
	Elevated	115 (66%)	1.457 (1.016; 2.089)	0.0406

ALT alanine aminotransferase, *HR* hazard ratio, *CI* confidence interval

Continuous variables/linear trend: HR > (<)1: higher (lower) risk for higher predictor level

Categorical variables: global *p*-value for any difference between groups

Binary variables/pairwise tests: HR > (<)1: higher (lower) risk for given category compared to reference

stage of MBC where patients had a median of 4 prior systemic treatments for metastatic disease before starting MMC and a 36.6 months interval between diagnosis of metastases and MMC infusion.

It may be important to select patients for MMC infusion that can have the most benefit of the treatment. For that reason, we performed a multivariable analysis of independent pre-treatment factors associated with OS. The independent factors associated with a poor survival were all related to extensive prior treatment and high tumour load in the liver accompanied with deteriorated laboratory liver tests. In the literature, previously reported factors for worse overall survival in LMBC patients were administration of previous therapy, higher number of metastatic locations and baseline liver dysfunction which is in line with our findings [24–27]. Patients that responded, by RECIST, to the therapy had a significantly longer OS, compared to patients that had PD or when no response assessment was possible. The very short OS of the patients without response assessment (1.4 months) shows that these patients probably did not responded to the therapy. Therefore, this early endpoint is useful to evaluate if continuation of the therapy is justified. This is rather opposite to response assessment in patients treated with systemic

chemotherapy where a literature based analysis of 24 trials reported only a moderate association between objective response rate and OS in patients treated with 2nd and 3th line chemotherapies [28].

Besides chemo infusion, other intra-arterial therapies are available for LMBC patients consisting of transarterial chemo embolization (TACE) and radioembolization (TARE) [10]. Inclusion criteria for TARE and TACE are more strict, compared to chemo infusion, resulting in less advanced diseased LMBC patients with longer median overall survival (6.6–13.6 and 4.6–47 months, respectively) [29–31]. For TACE, all grade adverse events are reported up to 71% of the patients with grade 3 ≥ adverse events in 34.7% of the patients [32, 33]. TARE is generally better tolerated than TACE, with adverse events grades around 44% [32]. Response rates whereby disease control is obtained after TARE and TACE differ widely from 52 to 99% and 40 to 83%, respectively [29–31].

Limitation of our study is the retrospective nature of this study, namely the retrospective assessment of the patient records for toxicity and response assessment. Next to that, response assessment was only possible in 132 of the 176 patients and assessment of hPFS was only possible in 107 of the 176 patients. Further, patients were included over a period of 17 years in a rapidly changing therapeutic landscape.

In conclusion, intra-arterial MMC infusion was able to obtain disease control in 58% of the LMBC patients (PR and SD) with a low toxicity profile. MV analysis showed a worse OS in patients with an increased amount of prior therapies, a higher liver tumour burden and elevated levels of bilirubin and ALT. Further prospective studies are needed to determine the exact place of intra-arterial MMC infusion and other intra-arterial therapies in LMBC patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The requirement for obtaining informed consent was waived by the ethics committee of our institute (S60596), due to the retrospective nature of this study. All authors approved the final manuscript.

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