

Sequential intra-arterial infusion of ^{90}Y -resin microspheres and mitomycin C in chemo refractory liver metastatic breast cancer patients: a single centre pilot study

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Background. The aim of the study was to evaluate the safety and feasibility of intra-arterial mitomycin C (MMC) infusion after selective internal radiation therapy (SIRT) using Yttrium-90 (^{90}Y) resin microspheres in liver metastatic breast cancer (LMBC) patients.

Patients and methods. The prospective pilot study included LMBC patients from 2012–2018. Patients first received infusion of ^{90}Y resin microspheres, after 6–8 weeks response to treatment was assessed by MRI, ^{18}F -FDG PET/CT and laboratory tests. After exclusion of progressive disease, MMC infusion was administrated 8 weeks later in different dose cohorts; A: 6 mg in 1 cycle, B: 12 mg in 2 cycles, C: 24 mg in 2 cycles and D: maximum of 72 mg in 6 cycles. In cohort D the response was evaluated after every 2 cycles and continued after exclusion of progressive disease. Adverse events (AE) were reported according to CTCAE version 5.0.

Results. Sixteen patients received ^{90}Y treatment. Four patients were excluded for MMC infusion, because of extra hepatic disease progression ($n = 3$) and clinical and biochemical instability ($n = 1$). That resulted in the following number of patient per cohort; A: 2, B: 1, C: 3 and D: 6. In 4 of the 12 patients (all cohort D) the maximum dose of MMC was adjusted due biochemical toxicities ($n = 2$) and progressive disease ($n = 2$). One grade 3 AE occurred after ^{90}Y treatment consisting of a gastrointestinal ulcer whereby prolonged hospitalization was needed.

Conclusions. Sequential treatment of intra-arterial infusion of MMC after ^{90}Y SIRT was feasible in 75% of the patients when MMC was administrated in different escalating dose cohorts. However, caution is needed to prevent reflux after ^{90}Y SIRT in LMBC patients.

Key words: liver metastatic breast cancer; chemo resistant; intra-arterial therapy; radioembolization; selective internal radiation therapy; mitomycin C infusion

Introduction

Up to 50% of the metastatic breast cancer (mBC) patients eventually develop liver metastases which

is associated with a poor overall survival ranging from 1–3 years.^{1,2} Liver metastatic breast cancer (LMBC) patients with limited (extra) hepatic disease can obtain a survival benefit from local

treatment options, such as surgery and ablation.^{3,4} Unfortunately, most LMBC patients have extended disease whereby systemic treatment by chemotherapy or anti-hormonal therapy, in hormone sensitive breast cancer, is indicated. Systemic treatment with chemotherapy has lengthened overall survival, but haematological, gastrointestinal and neurotoxicity are dose-limiting factors with systemic administration of these agents.⁵ Therapies with less systemic toxicity are therefore an attractive treatment option in LMBC patients refractory to systemic chemotherapy.⁶

Several intra-arterial therapies have been applied for LMBC patients, such as radioembolization (Yttrium-90 (^{90}Y) resin microspheres), chemo embolization and chemo infusion, reported as effective and safe treatment options.⁷⁻⁹ Of these treatments, the best results are reported for intra-arterial radioembolization, with a disease control rate of 72–91% and an overall survival of 6.6–13.6 months.^{7,10-12} For over 15 years, LMBC patients are treated by intra-arterial chemo infusion with mitomycin C (MMC) in our institute whereby disease control is obtained in 58% with low adverse events in a very heavily pre-treated cohort.⁹

Since primary breast cancer is sensitive for both systemic chemotherapy and external beam radiation therapy, LMBC patients might also benefit from the combined treatment of chemo infusion and selective internal radiation therapy (SIRT).

However, the sequential administration of these intra-arterial therapies *e.g.* SIRT and intra-arterial chemo infusion, has not yet been reported. In this pilot study we prospectively analysed the safety and feasibility of the sequential intra-arterial infusion of ^{90}Y resin microspheres and MMC in patients refractory to conventional systemic chemotherapy.

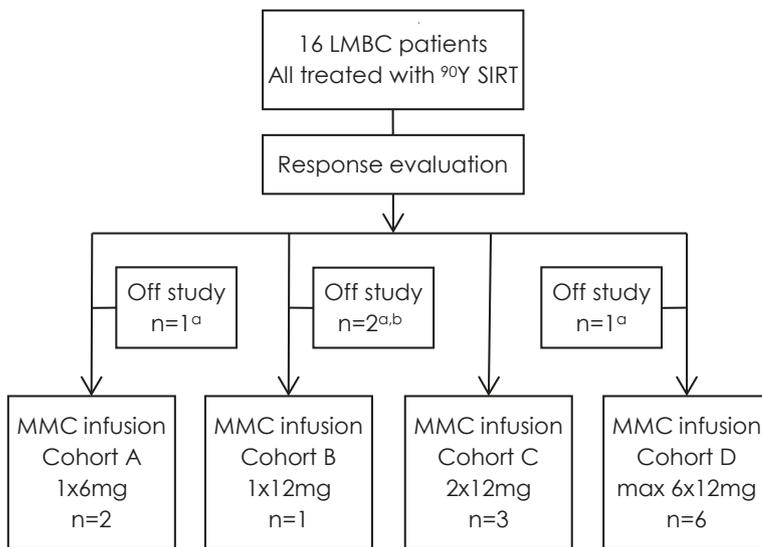
Patients and methods

This prospective phase I pilot study of 16 patients was approved by the ethics committee of our hospital (S 53657). Patients were included from April 2012 until March 2018. All patients signed a written informed consent. Patient selection was performed by a multidisciplinary tumour board consisting of medical, surgical and radiation oncologists together with pathologists, nuclear medicine physicians and (interventional) radiologists.

In Table 1, the inclusion and exclusion criteria for this pilot study are shown. Figure 1 shows the treatment schedule of ^{90}Y SIRT followed by MMC infusion in the different cohorts. The first 3 patients were allocated to cohort A, the second 3 patients to cohort B, the 3 patients thereafter to cohort C and the remaining of the patients in cohort D. Patients first underwent the ^{90}Y treatment and in the absence of progression, the sequential intra-arterial hepatic MMC infusions were administrated 8 weeks later.

Radioembolization with Yttrium-90 (^{90}Y) resin microspheres

All ^{90}Y procedures were performed under local anaesthesia by or under direct supervision of an expert interventional radiologist (GM) and nuclear medicine physician (CD). Previously published work describes the details of the ^{90}Y treatment.¹³ Briefly, patients first underwent a detailed baseline angiogram and embolization of enterohepatic arteries with micro-coils according to the expertise of the interventional radiologist. Technetium-99m-macroaggregated albumin ($^{99\text{m}}\text{Tc-MAA}$) was injected in the target vessels and a planar scintigraphy was performed to determine the lung shunt fraction. Two weeks later patients underwent bi-lobar or uni-lobar injection of ^{90}Y resin microspheres (SIR spheres[®], Sirtex Inc, Cosgrove, Australia) under local anaesthesia. The activity of ^{90}Y injected in the patient was calculated based on the body surface area method. In patients where it was possible to use the partition model, the partition model was used instead of the body surface area method. Dependent



^a Due to extra hepatic disease progression
^b Due the biochemical and clinical toxicities

FIGURE 1. Treatment overview of the 16 patients treated with selective internal radiation therapy with Yttrium-90 containing microspheres (^{90}Y SIRT) and mitomycin C (MMC) infusion in 4 escalating cohorts.

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Histologically confirmed diagnosis of breast cancer	Bilirubin level > 1.5x upper limit normal
Radiological evidence of liver metastases	Transaminase (AST/ALT) > 2.5x upper limit normal
Liver only or liver predominant with stable extra-hepatic disease	Creatinine > 1.2x upper limit normal
Progressive under (multi-line) systemic chemo or hormonal therapy	Glomerular filtration rate < 60 mL/min/1.73 m ²
Eligible for intra-arterial therapy	Neutrophils < 1000/μL
Age > 18 years	Thrombocytes < 100x10 ⁹ /L
Karnofsky performance > 70	Lung shunt fraction > 20%
	Allergy to contrast media
	Active use of oral anticoagulation

ALT = alanine aminotransferase; AST = aspartate aminotransferase

on the site of lesions, the ⁹⁰Y resin microspheres were injected intra-arterially via a micro catheter to the right and left liver lobe (superselective). A Progreat® micro catheter (Terumo, Europe) or an anti-reflux catheter (Surefire Inc., Westminster, CO, USA) was used for injection of the microspheres. Patients received antiemetics and morphine derivatives before ⁹⁰Y injection when required.

Hepatic intra-arterial chemo infusion with MMC

Six to eight weeks after the ⁹⁰Y treatment, patients underwent response assessment by magnetic resonance imaging (MRI) of the liver and a whole body [¹⁸F]-FDG positron emission tomography/computed tomography scan (¹⁸F-FDG PET/CT) together with laboratory tests. If patients showed no untreatable progression of disease on MRI and ¹⁸F-FDG PET-CT scan (bases on RECIST criteria 1.1) together with acceptable laboratory results (> 100x10⁹ thrombocytes/L), the intra-arterial chemo-infusion of MMC could be administrated. Six to ten weeks after the ⁹⁰Y procedure, patients received the first infusion of MMC, as previously described by our group.¹⁴ After local anaesthesia, vascular access was obtained by the right common femoral artery and, using a diagnostic 4-French catheter, a micro catheter was placed in the right and left hepatic arteries for injection of MMC in both liver lobes.

Ascending maximal doses of MMC were administrated in different cohorts. Patients were allocated to the MMC cohort before the ⁹⁰Y procedure. The first cohort (A) received one cycle of 6mg MMC, the second cohort (B) received one cycle of 12mg MMC, the third cohort (C) received 2

cycles of 12mg of MMC and the fourth cohort (D) received the standard regime of MMC infusion consisting of a maximum of 6 cycles of each 12mg of MMC. Before and after the MMC infusion laboratory results were taken to determine whether the dose could be tolerated. The dose of MMC was adjusted when thrombocyte count was < 100x10⁹ thrombocytes/L. In the last cohort, the effect of MMC was radiologically evaluated, by CT or MRI, after every two cycles. If these evaluations showed no further intra- or extra-hepatic disease progression, the patient was rescheduled for the next 2 cycles for a maximum of 6 cycles.

Outcomes

The primary outcomes of this study included the feasibility and safety of MMC infusion after ⁹⁰Y SIRT. The feasibility was defined as the number of patients receiving the MMC infusion after ⁹⁰Y treatment. The safety was determined by the number of grade 3 and higher adverse events after MMC and ⁹⁰Y treatment and documented by the Common Terminology Criteria for Adverse Events version 5.0. For the response assessment the modified response evaluation criteria in solid tumours (mRECIST) was used to measure hepatic response by a maximum of two target lesions and categorized into four categories [Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD)].¹⁵

Statistical analysis

Patient and pre-treatment characteristics were presented as numbers, percentages and median time

with range. Overall survival (OS) was calculated from work-up for ⁹⁰Y treatment until death or loss to follow up by the Kaplan Meier estimates. All analyses were performed in SPSS (IBM Corp, version 25, Armonk, NY).

Results

Patient characteristics

Table 2 shows the patient characteristics of the 16 treated women. The median time from diagnosis of metastatic breast cancer to start of the study was 28 months (range 7.7–91.0 months). Patients were 26–77 (median 59) years old at the start of the study.

TABLE 2. Patient characteristics

Patient Characteristics	N = 16
Median months from diagnosis metastatic disease until start of study	28 (8–91)
Median age at start study in years (range)	59 (26–77)
Diagnosis of liver metastasis	
Synchronous	2 (12.5%)
Metachronous	14 (87.5%)
Hormone status of liver metastasis (n = 15)	
Estrogen receptor (positive)	8 (53%)
Progesterone receptor (positive)	8 (53%)
HER2Neu receptor (negative)	15 (100%)
Triple negative receptor status	6 (40%)
Tumor burden liver	
< 25%	9 (56%)
25%–50%	6 (38%)
50%–75%	1 (6%)
Prior hepatic treatment	
Surgery/Ablation	1 (6.3%)
Median number of chemotherapy regimens for stage 4 disease	3 (0–8)
Extra-hepatic sites of metastases	
Yes	9 (56%)
No	7 (44%)
Number of additional metastatic sites	
1	5 (31%)
2	2 (13%)
≥ 3	2 (13%)
Location of extrahepatic metastases	
Bone	5 (31%)
Lung	3 (19%)
Non-locoregional nodes	4 (25%)
Brain	2 (13%)

A liver biopsy was taken before start of the study in 15 patients and showed a positive oestrogen receptor in 8 patients, positive progesterone receptor in 8 patients and a negative HER2-neu status in all patients (n = 15). Six patients had a triple negative receptor status. Tumour burden of the liver was < 25% in 9 patients and > 25% in 7 patients. Nine patients had extra-hepatic disease with a median of 1 site (range 0–4) and bone (n = 5) as most common site. Before inclusion, the median number of chemotherapy lines in the metastatic phase was 3 regimes consisting of anthracyclines in 75% and taxanes in 81%.

Treatment

Figure 1 shows a treatment overview of the 16 patients. All 16 patients underwent the ⁹⁰Y procedure whereby pre-embolization of extra hepatic arteries was performed in 14/16 patients. A median dose of 1.68 GBq (range 1.043–2.140) was inserted in both liver lobes (n = 14) or one liver lobe (n = 2). At response evaluation five patients showed extra-hepatic disease progression, of whom, three patients were excluded for additional MMC infusion and two patients received the sequential MMC infusion, but with additional therapy of Exemestane (Aromasin®) for stabilization of their extra-hepatic disease. One patient was hospitalized after ⁹⁰Y SIRT for 2.5 weeks because of the side effects of the ⁹⁰Y treatment and excluded from further treatment.

Median time between ⁹⁰Y SIRT and first MMC infusion was 2.1 months (range 1.7–12.8 months). In one patient an interval of 12.8 months occurred, because of PD in the liver after ⁹⁰Y treatment. This patient first received systemic chemotherapy and after progression during this systemic chemotherapy the MMC infusion was administrated. A total of 12 patients were treated in four different cohorts of MMC doses after the ⁹⁰Y treatment (Figure 1). In cohort D, the maximum of 6 cycles of 12 mg MMC was administrated in 2 patients. In the other four patients the dose was adjusted (n = 2) and discontinued (n = 2) due to hematologic toxicity (thrombocytopenia) and disease progression.

Adverse events

Table 3 shows the adverse events after the ⁹⁰Y SIRT and MMC infusion. After the ⁹⁰Y treatment one grade 3 adverse event occurred, consisted of a gastric ulcer treated with proton pump inhibitors and hospitalization. The most common grade 1/2 adverse events after ⁹⁰Y SIRT were pain 7/16, nausea

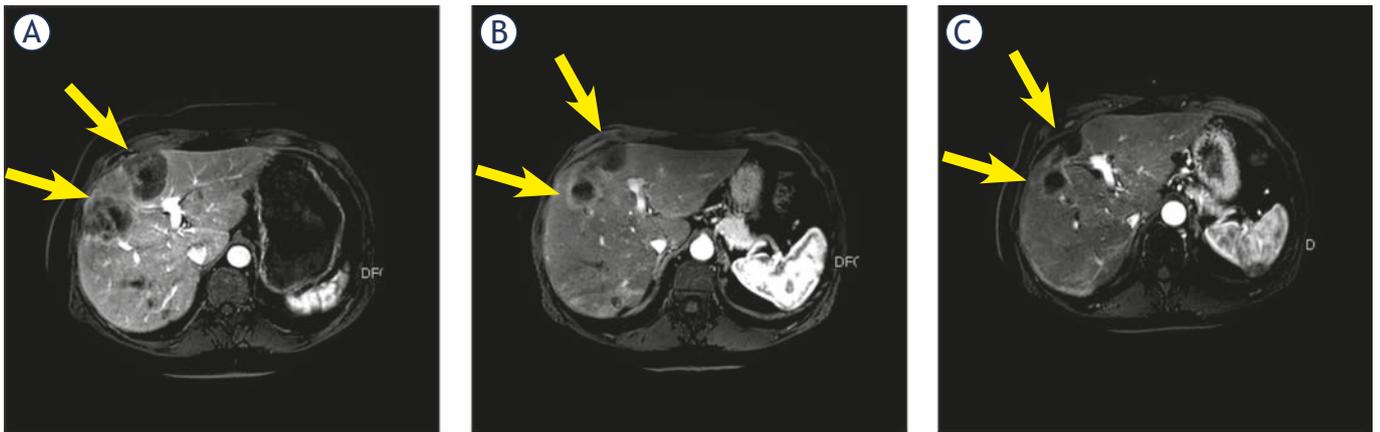


FIGURE 2. Hepatic response on magnetic resonance imaging (MRI) before ⁹⁰Y treatment (A), after ⁹⁰Y treatment (B) and after 2 cycles of MMC infusion (C). C is a partial response relative to A. Arrows indicate the liver metastases.

5/16 and ulcer 4/16. An elevation in liver function test (aspartate, alanine and gamma-glutamyl transferase) was seen in 8/16 patients.

No grade 3 or higher adverse events occurred after MMC infusion. The most common grade 1/2 adverse event was thrombocytopenia in 11/12 patients and leukopenia in 8/12 patients.

Response, follow up and survival

Response evaluation of the liver after 6 to 8 weeks after ⁹⁰Y treatment (n = 16) revealed PR in 10 patients and SD in 6 patients (Figure 2). Extra hepatic response evaluation showed PD in 5 patients and SD in 11 patients. Additional hepatic response of

TABLE 3. Number of grade 1 (G1), grade 2 (G2) and grade 3 (G3) adverse events after treatment of selective internal radiation therapy by ⁹⁰Y labeled microspheres infusion (⁹⁰Y SIRT) and mitomycin C (MMC) infusion within 30 days. No grade 3 adverse events occurred after MMC infusion

Treatment	⁹⁰ Y SIRT			MMC Cohort A 1x6mg		MMC Cohort B 1x12mg		MMC Cohort C 2x12 mg		MMC Cohort D max 6x12mg	
	G1	G2	G3	G1	G2	G1	G2	G1	G2	G1	G2
Adverse events											
Clinical											
Fatigue	2/16	-	-	-	-	-	-	3/3	-	2/6	-
Pain	5/16	2/16	-	-	-	-	-	-	-	1/6	-
Nausea	3/16	2/16	-	-	-	-	-	-	-	1/6	-
Emesis	2/16	2/16	-	-	-	-	-	-	-	1/6	-
Gastrointestinal ulcer	-	4/16	1/16	-	-	-	-	-	-	-	-
Biochemical											
Leukopenia	2/16	-	-	-	-	-	-	2/3	-	4/6	2/6
Thrombocytopenia	3/16	1/16	-	1/2	-	1/1	-	3/3	-	4/6	2/6
Anaemia	-	-	-	-	-	-	-	-	-	4/6	-
Increased aspartate aminotransferase	5/16	1/16	-	-	-	-	-	-	-	2/6	-
Increased alanine aminotransferase	3/16	1/16	-	-	-	-	-	-	-	1/6	-
Increased bilirubin	-	-	-	-	-	-	-	1/3	1/3	-	-
Increased alkaline phosphatase	2/16	1/16	-	-	-	-	-	1/3	-	2/6	-
Decreased eGFR	-	1/16	-	-	-	-	-	-	-	-	-
Increased gamma-glutamyl transferase	4/16	1/16	-	-	-	-	-	1/3	-	4/6	-

eGFR = estimated glomerular filtration rate

MMC infusion after ^{90}Y treatment was PR in 4/12 patient, SD in 5/12 patients and PD in 3/12 patients.

After the study, nine patients were eligible to receive systemic chemotherapy and one patient was eligible for surgery and underwent a segmentectomy. The median OS was 12.6 months (95% CI 10.23–15.0).

Discussion

Intra-arterial therapy is a treatment option in patients with chemo-refractory liver dominant metastatic breast cancer.⁶ In our institute MMC infusions are performed for almost 20 years for chemo refractory LMBC whereby a disease control of 58% is obtained with low grade adverse events.⁹ In the present study we investigated whether MMC infusion is feasible and safe after ^{90}Y SIRT.

The sequential treatment of ^{90}Y followed by MMC was possible in 75% (12/16) of the enrolled patients. Only low-grade adverse events (grade 1 and 2) were observed after the MMC infusions. In addition, the gradual escalation of the MMC infusions, ranging from 6 mg in 1 cycle to a maximum of 72 mg in 6 cycles, caused no additional adverse events.

During the regular MMC protocol of our institute, patients can receive a maximum of 72 mg in 6 cycles whereby close monitoring is performed to adjust, postpone or stop the MMC infusion after each cycle.⁹ In current study, the same protocol was followed in the last cohort, subsequently 4 patients did not receive all 6 MMC cycles. Thus, this pilot shows that the regular protocol of MMC can be followed after prior treatment with ^{90}Y . Patients maintained their performance status after the sequential treatments, and so 9/12 patients were eligible for systemic therapy afterwards and 1/12 even for hepatic surgery. Therefore, this combination treatment can be used as a drug holiday from systemic treatment.

We did observe a high number of gastrointestinal ulcers after ^{90}Y SIRT ($n = 5$, 31%). All these patients underwent pre-embolization and received a bilobar treatment in the left and right hepatic artery. Despite these precautions, the ulcers occurred probably due to reflux and non-target deposition of the ^{90}Y resin microspheres which is a known risk of ^{90}Y treatment for LMBC.¹⁶ After the introduction of an anti-reflux catheter in the last 6 patients, no more ulcers occurred. According to the literature, several factors are associated with reflux of ^{90}Y resulting in gastrointestinal ulceration, namely

prior administration of monoclonal antibodies (*i.e.* bevacuzimab, trastuzumab), the type of ^{90}Y microspheres and the dose of ^{90}Y .^{10,17} In the present study no correlations were found for prior monoclonal antibodies treatment and the dose of ^{90}Y with the development of gastrointestinal ulcers. The development of the gastrointestinal ulcers in the current study was probably caused by several pre-treatment and treatment related factors. The use of the anti-reflux catheter showed improvement with no further reported gastrointestinal ulceration. Therefore, caution is needed in future studies.

The median OS of radioembolization in LMBC patients ranges from 6.6–13.6 months, which is in line with the median OS of 12.6 in this study.^{10,11,18-20} The median OS was higher compared to earlier studies where patients received only MMC infusion (12.6 versus 7.6 months).^{9,14} However, the inclusion criteria for this study were more strict than our routine indications for MMC infusion. Consequently, patients had less extensive local and extra hepatic disease with a better performance status compared to our previous reported cohort of patients treated with MMC infusion only.

The main limitation of this study consists of small patient number in the cohorts and the long inclusion period.

Conclusions

In conclusion, the sequential treatment of intra-arterial infusion of MMC after ^{90}Y therapy is feasible with limited low-grade adverse events after MMC. The regular MMC protocol can be followed with adjustment of MMC dose based on clinical, radiological and biochemical parameters. However, caution is needed to prevent reflux after ^{90}Y SIRT in LMBC patients. Further research is needed to show whether the combination of ^{90}Y and MMC has a benefit over the treatment of MMC or ^{90}Y alone in LMBC patients.

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