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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Chemoembolization with Degradable Starch Microspheres for Treatment of Patients with Primary or Recurrent Unresectable, Locally Advanced Intrahepatic Cholangiocarcinoma: A Pilot Study

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Abstract

Purpose To evaluate efficacy and complication rates of TACE with degradable starch microspheres (DSM-TACE) in patients with unresectable intrahepatic cholangiocarcinoma (ICC) with or without prior major liver resection (MLR).

Methods This is a retrospective single-center study on 21 patients (age 63 ± 15 years) with either unresectable ICC progressive under systemic chemotherapy or unresectable intrahepatic tumor recurrence after prior MLR. Patients were treated by multi-agent (cisplatin/doxorubicin/mitomycin C) DSM-TACE between August 2012 and July 2016, repeated 3 times at 4-week intervals. Imaging response was evaluated using RECIST 1.1. Overall survival (OS) and complication rates, stratified by history of MLR, were investigated.

Results Patients underwent a total 64 DSM-TACE sessions. Two patients (without MLR) were lost to follow-up after one uneventful DSM-TACE session. One patient underwent living-donor-liver transplantation after one DSM-TACE-session yielding partial remission. Of the remaining 18 patients, imaging response according to RECIST 1.1 was: complete remission in 2/18 (11.1%); PR in 9/18 (50%), and stable disease in 7/18 (38.9%), yielding an objective response rate of 61.1% and a disease control rate of 100%. Median OS of patients with objective response was significantly longer (18.0 months) than that of survival of patients with stable disease (4.8 months) ($p = 0.001$). Median OS of patients with MLR (12.5 months) was similar to that of patients without MLR (13.2 months). Of 21 patients, 2 (9.5%) developed post-interventional hepatobiliary abscesses, and one of these patients died due to subsequent sepsis.

Conclusion DSM-TACE is an effective treatment for unresectable and otherwise therapy-refractory intrahepatic cholangiocarcinoma, even in those patients with intrahepatic disease recurrence after prior MLR.

Level of Evidence Level II, therapeutic study.

Introduction

Cholangiocarcinoma, a primary hepatic malignancy that arises from the epithelial cells of bile ducts, is observed with increasing incidence [1]. Depending on the site of origin within the biliary tree, intrahepatic and peripheral cholangiocarcinomas are distinguished. Intrahepatic cholangiocarcinomas (ICC) represent about 5–15% of all cholangiocarcinomas [2]. The median survival of patients with untreated ICC ranges between 3 and 9 months [3]. Surgery represents the only curative treatment option and is therefore the mainstay of treatment for ICC. However, even when radical surgery achieves tumor-free resection margins, survival is limited to a mean of 27 months, and

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the 5-year-survival rate is about 30% [4]. Additionally, only a minority of patients—usually between 30 and 40%—are resectable at the time of diagnosis [5]. Moreover, in patients who are able to undergo surgery, the most common site of recurrence is the liver after a median disease-free survival between 12 and 26 months [6, 7]. Patients who develop such intrahepatic recurrence will be inoperable in the majority of cases [8].

In patients not suited for surgery or who recur after hepatic surgery, minimally invasive local treatment strategies have been proposed to achieve local tumor control. If the recurrent tumor load is small, local ablation or percutaneous brachytherapy has been shown to be useful treatment options [9, 10]. However, in patients with large, multi-focal or diffuse recurrent disease, regional, i.e., trans-arterial, treatment options have been pursued. Both chemoembolization and radioembolization have been demonstrated to be effective [11, 12].

In this study, we report on our experiences with the use of a trans-arterial multi-agent chemotherapy with degradable starch microspheres (DSM-TACE) for treatment for primary or recurrent, locally advanced, unresectable ICC.

Material and Methods

The need to submit the study protocol for an ethics committee review was waived by the Institutional Review Board (IRB) due to the retrospective nature of this study.

Study Cohort

Between August 2012 and July 2016, a total of 21 consecutive patients (4 female, 17 male; mean age 61 years; range 30–82 years) with locally advanced, unresectable ICC with or without a history of prior major liver resection underwent DSM-TACE at our institution. Out of these 21 patients, two patients were lost to follow-up after one TACE session and one patient underwent living-donor-liver transplantation 4 weeks after the first TACE, leaving a total of 18 patients who were included in the final survival and response analysis. Patient demographics are shown in Table 1.

Eligibility for DSM-TACE

Patients meeting the following criteria were considered candidates for DSM-TACE:

Patients with histologically proven, primary unresectable ICC who developed progressive disease in spite of systemic chemotherapy or patients with multi-focal intrahepatic recurrence after prior hepatic resection who were considered unresectable and not amenable to treatment by local ablation. Further eligibility criteria included a hepatic tumor burden occupying less than 75% of the liver or liver remnant and a preserved liver function (Child–Pugh A or B, bilirubin level < 2 mg/dl and INR < 1.5). Additionally, only patients without extrahepatic disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were considered for DSM-TACE treatment.

All treatment decisions (surgical, local or systemic) were established by consensus by a multi-disciplinary tumor board consisting of hepatobiliary surgeons, gastroenterologists, oncologists, radiation oncologists, pathologists and interventional radiologists.

TACE Procedure

Written informed consent was obtained from all patients before the procedures. All TACE procedures followed a standardized protocol and were performed by one of three interventional radiologists with 23, 11 and 6 years of experience in TACE procedures. Angiography was performed after selective catheterization of the celiac trunc, the common hepatic artery and the proper hepatic artery with a 5F catheter (Cobra or Sidewinder configuration; Cook Medical LLC, Bloomington, IN USA; Merit Medical Systems, South Jordan, UT USA) to define or confirm CT diagnoses of the patient's individual arterial anatomy and to outline the intrahepatic distribution of tumor load and identify the feeding lobar or segmental hepatic artery branches. A 2.4F or 2.7F microcatheter (Progreat, Terumo Corporation, Tokyo, Japan; Renegade, Boston Scientific Corporation, Marlborough, MA, USA) was advanced distally, depending on the desired liver volume to be treated. Then, segmental or lobar contrast-enhanced cone beam CT (CBCT) was acquired in the late-arterial phase to define the distribution volume of the intubated vessel [13].

DSM-TACE was performed in a lobar or segmental approach depending on the distribution of intrahepatic tumor load. In patients with bilobar disease, whole-liver treatment with a total dosage of 100 mg cisplatin, 50 mg doxorubicin and 10 mg mitomycin C was administered into the lobar hepatic arteries (ratio left/right: 35%/65% or 30%/70% depending on the size of the left liver lobe). Both lobar and bilobar treatments were performed in one session.

Controlled infusion of cisplatin with a flow rate of 2 mg/min was followed by manual injection of a mixture containing doxorubicin, mitomycin C and degradable starch microspheres with a mean diameter of 50 µm (range 20–70 µm) (EmboCept S, PharmaCept GmbH, Berlin,

Table 1 Description of the study cohort

Age		
Range	35–86	
Median	62	
Sex	*n*	%
Male	5	24
Female	16	76
Previous treatment prior to study inclusion	*n*	%
Surgery	12/21	57
Systemic chemotherapy	12/21	57
Type of surgical treatment	*n*	%
Multiple segmentectomies	5/12	42
Hemihepatectomy	4/12	33
Trisectorectomy	3/12	25
Type of chemotherapy	*n*	%
Cisplatin	0/12	0
Gemcitabine	2/12	17
Cisplatin plus Gemcitabine	9/12	75
Other	1/12	8
Affected liver	*n*	%
One lobe	3	14
Bilobar	11	52
Whole-liver remnant	7	33
Tumor extent within affected liver	n	%
Up to 25%	10	57
> 25–50%	8	29
> 50–75%	3	14
Known pre-existing liver diseases	*n*	%
Hepatitis B	1/21	5
Hepatitis C	0/21	0
PSC	0/21	0
Other biliary disease (e.g., Caroli)	0/21	0
None	20/21	95
Bilirubin levels at study inclusion (mg/dl)		
Mean	0.59	
Range	0.2–1.5	
No. of patients with elevated bilirubin level at study inclusion (> 1.2 mg/dl)	*n*	%
	2/21	10
INR levels at study inclusion	*n*	%
Mean	1.04	
Range	0.88–1.26	
No. of patients with abnormal INR at study inclusion (> 1.15)	n	%
	4/21	19

Germany) in combination with contrast agent under fluoroscopic control. Intermittent angiograms were performed to check for persistent antegrade flow, thereby avoiding backflow and non-target embolization. The technical endpoint of each treatment session was a significant reduction of blood flow in the tumor feeding vessels, i.e., a near-stasis in segmental arteries and loss of tumor blush on angiograms.

All patients received i.v. antiemetic and pain medication (8 mg ondansetron, 7.5–15 mg piritramid) as well as i.v. single-shot antibiotics (3 g sultamicillin). Eight milligrams of dexamethasone was given before injection of the cytotoxic agents and at 8 h and 16 h after TACE. All patients with bilioenteric anastomoses received a prophylactic antibiotic treatment prior to and for at least 2 weeks after treatment (e.g., oral acylaminopenicillins or

fluoroquinolones). All adverse events, either clinical or subclinical imaging findings, were recorded.

Treatment Schedule and Follow-up

The standard treatment schedule encompassed three DSM-TACE sessions at 4-week intervals; additional treatment sessions thereafter were considered whenever patients developed progressive disease during follow-up despite positive initial response to the DSM-TACE treatment. Liver imaging was done at baseline and before each TACE session by contrast-enhanced, four-phase CT or MRI including liver-specific contrast agent.

For further follow-up, patients were seen clinically 4 weeks after the last TACE and then every 3 months. At these points, laboratory analysis including liver function tests, tumor markers and complete blood count was done, and tumor response was assessed by liver MRI including liver-specific contrast agents or four-phase helical CT. Systemic staging by whole-body CT was done before start of treatment and every 6 months thereafter, or whenever clinical or laboratory findings (e.g., CA19-9 increase) suggested systemic progression.

Response Assessment

All MR and CT image data of each patient were systematically analyzed in a three-reader consensus with 23, 10 and 5 years of experience in TACE and liver MR and CT imaging. Response to TACE was evaluated using the RECIST 1.1 criteria. We determined the "best local response" to TACE during the follow-up, regardless of whether this was achieved after the first, the second or after several TACE sessions. Additionally, we determined rates of objective response [i.e., rates of complete remission (CR) and partial remission (PR)] and of disease control [i.e., rates of CR, PR and stable disease (SD)].

Data Analysis and Statistical Analysis

Continuous variables are expressed as mean values ± standard deviation and range. All test results were analyzed in an explorative way; thus, p-values of $p \leq 0.05$ were regarded as statistically significant. All statistical analyses were conducted using the Statistical Analysis System (SAS Version 9.2; SAS Institute, Cary, NC, USA) and R (R Version 2.11.1. Copyright (C) 2010 The R Foundation for Statistical Computing). Survival was calculated from time of first treatment. Median overall survival times and their respective 0.95% confidence intervals (0.95-CI) were estimated according to the Kaplan–Meier method. The respective last date of contact was counted as censored observation. Response to treatment was analyzed for an association with overall survival by performing the log-rank test.

Results

Treatment Details

The 18 patients who were included in the final analyses underwent a mean of 3.4 sessions per patient for a total of 61 treatment sessions. Three patients experienced adverse events after one TACE session and two others after the second treatment session and therefore did not complete all three planned treatment sessions. Two patients received one extra session, two others two extra sessions, and one 9 extra sessions after developing progressive disease during follow-up after initially responding well to the TACE treatments.

Best Tumor Response According to RECIST 1.1

For the 18 patients for whom long-term follow-up was available, the respective best local response according to RECIST 1.1 is provided in Table 2 and Fig. 1. The "objective response rate" (CR and PR) was 61% (11/18 patients), and the disease control rate (CR, PR and SD) was 100% (18/18 patients).

Time to Progression

Intrahepatic disease progression after DSM-TACE was seen in 7/18 patients, after a mean time of 9.5 ± 6.2 months (range 2.7–22.1 months) after the first TACE treatment. Systematic whole-body staging examinations conducted during follow-up exhibited extrahepatic disease progression in 11/18 patients. Mean time to extrahepatic progression was 6.7 ± 7.3 months after the first TACE (range 0.8–25.6 months). Extrahepatic disease developed mainly in the lungs (3 patients) and in the regional lymph nodes (4 patients).

Survival Analysis

Median overall survival of the 18 patients was 13.3 months (0.95-CI 8.9–17.7 months), with survival rates of 55.6% (10/18) at 1 year, 27.8% (5/18) at 2 years, and 5.6% (1/18) at 3 years. Causes of death for the 8 patients who died

Table 2 Detailed information on response for all patients depending on type of prior surgical treatment

Patient no	Type of prior surgery	Best response after TACE according to RECIST 1.1	Time to best response (months)	Time to progression (months)	Intrahepatic progression	Extrahepatic progression
1	HH	PR	0.9	No progression	No	No
2	None	SD	1.3	1.3	No	Peritoneal
3	MS	PR	2.3	5.1	No	Pancreas
4	None	PR	1.7	4.6	Yes	LN + adrenal
5	HH	PR	2.5	7.7	Yes	Lung
6	Tri	CR	3.4	25.6	No	Brain
7	None	SD	1.8	No progression	No	No
8	Tri	CR	4.6	8.9	No	LN
9	MS	PR	1.3	No progression	No	No
10	None	SD	2.3	7.0	Yes	LN
11	None	SD	1.0	1.0	No	Bone
12	MS	PR	3.0	8.5	Yes	LN
13	HH	PR	2.9	1.3	No	Lung
14	HH	SD	4.1	22.1	Yes	No
15	MS	PR	2.7	0.9	No	Lung
16	MS	PR	3.2	6.0	Yes	No
17	None	SD	1.2	No progression	No	No
18	Tri	SD	1.4	2.7	Yes	No
19*	None	PR	Not known (LTx @ 4 weeks after TACE)	22.2	N.a	Lung
20*	None	Lost to follow–up	Not known	Not known	Not known	Not known
21*	None	Lost to follow–up	Not known	Not known	Not known	Not known

Patients with asterisk were not included in the response analysis

HH hemihepatectomy, *MS* multiple segmentectomies, *Tri* trisectorectomy, *PR,* partial response, *SD* stable disease, *CR* complete response, *LTx* liver transplantation, *LN* lymph node

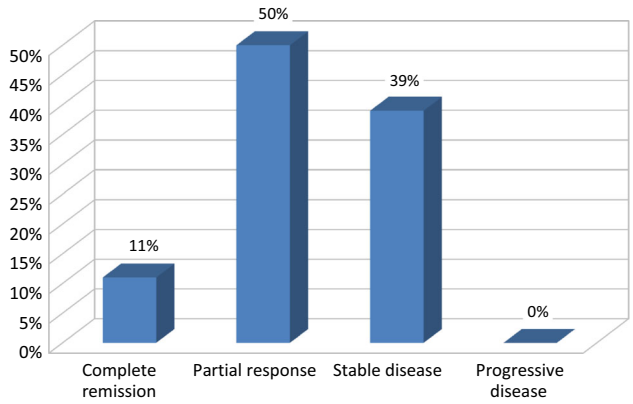

Fig. 1 Rates of best response observed according to RECIST 1.1

within the first year included (extrahepatic) tumor progression in three patients and sepsis from biliary abscesses, pulmonary sepsis and myocardial infarction in one patient each. In the remaining two patients, the cause of death was unknown. Overall survival of patients with objective response (CR + PR) was significantly longer (18.0 months, 0.95-CI 6.0–30.0 months) than survival of patients with SD (4.8 months, 0.95-CI 3.0–6.6 months) ($p = 0.001$) (Fig. 2). Survival of patients who had undergone prior hepatic surgery (13.1 months, 0.95-CI 8.4–17.8 months) was similar to that of patients who had not (12.5 months, 0.95-CI 2.5–22.5 months) (Fig. 3).

Adverse Events

A total of 5 adverse events (AE) were observed: 2 patient deaths, 1 severe AE and 2 mild AEs. The two lethal complications were as follows: one patient with a history of prior major liver surgery including a bilioenteric anastomosis presented with severe pyogenic liver abscess ten days after the first TACE (Fig. 4). The patient had not received the antibiotic treatment as prescribed. Despite intensive care treatment and CT-guided drainage of the abscesses, the patient died 1 month later due to multiple

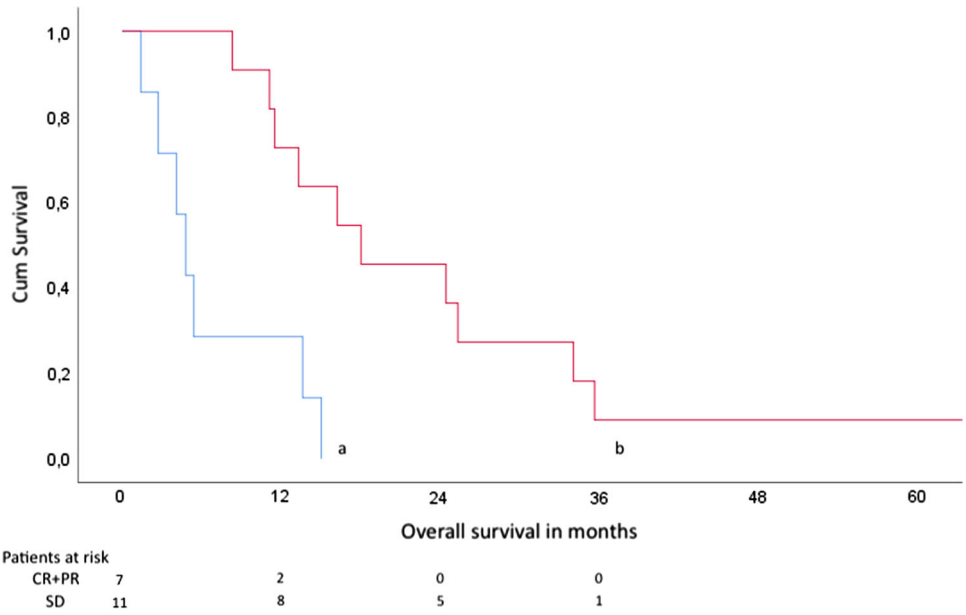

Fig. 2 Kaplan–Meyer statistics of patients with **a** stable disease versus and **b** patients with objective response (CR, PR). Survival times were statistically significantly shorter ($p = 0.001$) for patients with stable disease (**a**) versus those with complete or partial response, with median overall survival of 4.8 months (**a**) versus 18.0 months (**b**)

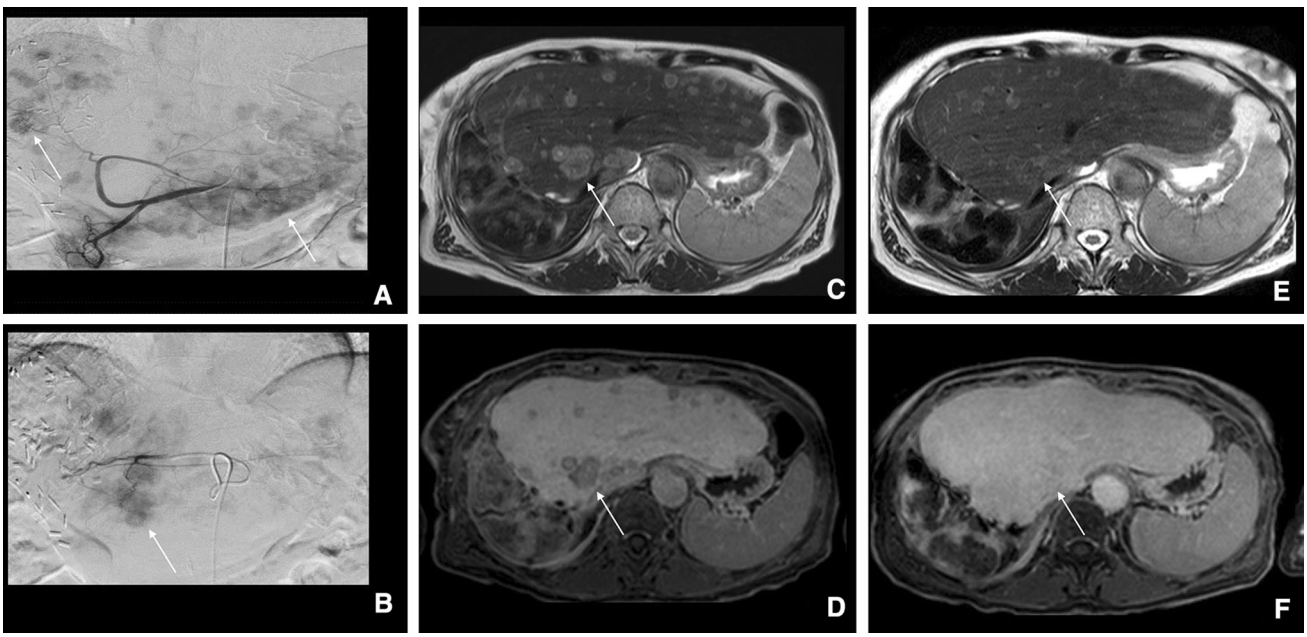

Fig. 3 DSM-TACE of a patient with recurrent ICC after hemihepatectomy. A 60-year-old female patient with intrahepatic recurrence of an ICC after right hemihepatectomy exhibited recurrent intrahepatic disease that was progressive under systemic chemotherapy. Angiography during first session of TACE via the common hepatic artery (**a**) and aberrant left hepatic artery originating from the gastric artery (**b**) shows extensive, hypervascular tumor in all segments (white arrows). Pre-interventional baseline MRI with **c** T2-w TSE imaging and **d** T1-w FFE in the hepatocyte phase after Gd-EOB-DTPA demonstrates diffusely recurrent intrahepatic ICC, for example, in liver segment IVa (white arrows). At 4-month follow-up after 3 sessions of DSM-TACE, **e** T2w-TSE and **f** hepatobiliary MRI, there was an almost complete reduction of vital tumor load; the lesion in segment IVa is barely visible (white arrows). This case was considered "partial response"

organ failure. The second patient, without prior liver surgery, developed a sudden cardiac arrest just before his third TACE caused by coronary ischemia; the patient died 2 days later in spite of intensive care treatment; based on the cardiologists' assessment, the death was unlikely to be related to the procedure. The one severe AE was observed in a patient who developed bile duct necrosis and hepatobiliary abscess formation after his second TACE, requiring hospitalization and repetitive drainage during two separate hospital stays. Procedure-associated mild AEs occurred in two patients after the first TACE, in whom asymptomatic peribiliary necrosis was detected on routine follow-up

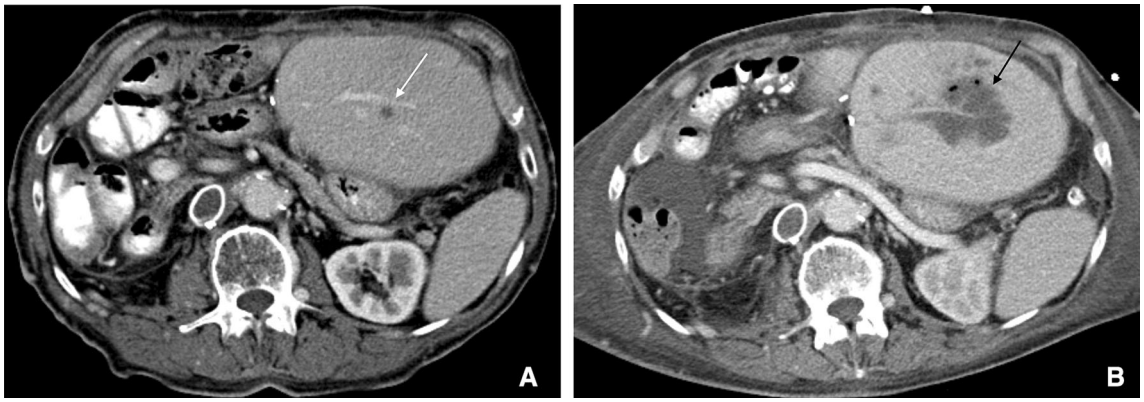

Fig. 4 Hepatic abscess after TACE. 70-year-old male patient with multi-focal recurrence of an intrahepatic cholangiocellular carcinoma after right hemihepatectomy. On the pre-interventional CT scan (**a**), there were several small ICC nodules (white arrow) spread throughout the liver remnant. 10 days after the first TACE, the patient returned with fever and upper abdominal tenderness and a CT scan (**b**) revealed multiple hepatic abscesses (black arrow). Despite subsequent treatment with drainage of the abscesses and antibiotics, the patient died 1 month later of septic multi-organ failure

imaging, without clinical signs or symptoms of superinfection. Continued antibiotic treatment was administered in these cases, and as a precautionary measure, these patients did not undergo additional treatment sessions to avoid further aggravation of the necroses.

Discussion

In this case series of patients with primary or recurrent intrahepatic ICC, refractory to systemic chemotherapy, unresectable and not amenable to ablation, multi-session trans-arterial multi-agent chemoembolization therapy with degradable starch microspheres proved to be an effective treatment method that was generally well tolerated. With an objective response rate of 61% (11/18) for response assessment according to RECIST 1.1 and with disease control achieved at least temporarily in all 18 patients for whom long-term follow-up is available, the response rates observed in this cohort were encouraging. Since overall survival improved with the degree of response, there is reason to assume that DSM-TACE treatment does improve survival in ICC. Observed results are particularly remarkable in view of the highly palliative situation of the patients included in this study, who were refractory to or not amenable to other types of treatment.

Since the majority of patients with ICC are inoperable at the time of diagnosis or develop local recurrence after liver surgery, there is a substantial clinical need for effective local treatment strategies to ensure disease control. Objective response rates of DSM-TACE observed in this small cohort (61%) compare favorably with the objective response rates of 0%, 7%, 9% and 23% published for conventional TACE in other cohorts with intrahepatic CC [3, 14–16]. Response rates observed after Y90-radioembolization (Y90-RE) have been consistently marginally higher (11–26%), but are still lower than the response rates observed in this study [12, 17–20]. An advantage of radioembolization compared with DSM-TACE is the fact that Y90-RE usually requires only a single treatment session as opposed to several sessions of DSM-TACE. On the other hand, DSM-TACE employs chemotherapeutic agents that would be indicated for systemic treatment in the same situation according to established oncological guidelines; in a patient with liver-only or liver-dominant disease, such liver-directed application of clinically established chemotherapeutic agents is a logical step.

The rationale to use the 20–70 μm-sized DSM for TACE of ICC is to combine the concept of chemoembolization with the concept of systemic chemotherapy: Coupling the chemotherapeutic agent to an embolic agent which causes only temporary and distal capillary occlusion leads to higher intra-tumoral concentrations of chemotherapeutic agents [21] while also leaving the trans-arterial route patent for repeated treatments according to the principles of systemic chemotherapy cycles. In contrast, other embolic agents may either lead to permanent vessel occlusions and thus interfere with the ability to repeat the treatment (microspheres) or lead to temporary occlusion of larger vessels without the desired effect on intra-tumoral chemotherapeutic concentrations (gelatin sponge). DSM-TACE has previously been successfully used in patients with HCC and liver metastases of renal cell, colorectal and breast cancer [22–25]. Published experiences with DSM-TACE of patients with ICC so far involve very small numbers of patients, different chemotherapeutic regimens and focus mainly on procedural safety [24, 26–28]. The chemotherapeutic regimen used in this study—50 mg doxorubicin, 100 mg cisplatin and

10 mg mitomycin C—has been successfully used elsewhere for trans-arterial treatment for ICCs in combination with other embolic agents, and therefore, we chose to use this regimen in combination with DSM [11, 29].

An important finding of this study is the potential risk of peribiliary necrosis when using DSM-TACE in patients with ICC, which is most likely the result of embolization of small peribiliary capillaries. Two out of 21 patients (9.5%) developed superinfected hepatobiliary abscesses after DSM-TACE requiring drainage, and eventually, one of these two patients died due to subsequent sepsis and multi-organ failure. This emphasizes the need for careful surveillance and early anti-infective or preventive antibiotic treatment, especially in high-risk patients with a bilioenteric anastomosis.

Important limitations of this study include the retrospective study design and the small size of the cohort as well as the lack of a control group. Therefore, the reliability of all statistical analyses is low and no definitive conclusions can be drawn about a potential recurrence-free and overall survival benefit compared to best supportive care.

However, the greatly encouraging results led to the decision to publish these data at this stage, to justify and help with the design of a prospective trial on second-line DSM-TACE treatment of patients with ICC, preferably as a randomized control trial versus Y^{90} radioembolization which represents another trans-arterial treatment option in these patients.

In conclusion, in this small cohort of patients, DSM-TACE appears to be an effective palliative treatment option in patients with unresectable intrahepatic ICC who do not respond to systemic treatment and in those with unresectable recurrence after prior liver resection. Considering the increased risk of peribiliary necrosis and subsequent hepatobiliary abscess development, precautionary measures, i.e., prophylactic antibiotics, should be strongly considered, especially in patients with a bilioenteric anastomosis. The results of this study should be validated in a larger prospective clinical trial on the palliative treatment of patients with inoperable ICC.

Compliance with Ethical Standards

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

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