EXPERIENCE IN TREATMENT OF COLORECTAL LIVER METASTASES

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More than 30 % of patients with colorectal cancer developed liver metastases. Radical surgical resection of liver metastases remains the only chance of cure with more than 50% 5-year survival. Unfortunately, most of the patients are presented with unresectable metastases because of their size, number, location or inadequate liver remnant after resection.

In unresectable disease, many ablative approaches can be used. The most frequent is radiofrequency ablation(RFA). However, RFA is less effective in the treatment of metastases in the vicinity of major hepatic vessels due to heat sink effect.

From 2009 to 2018 35 patients with colorectal liver metastases were treated with electrochemoterapy at our department. In our first published analyses, 29 metastases in 16 patients were treated with electrochemoterapy during open surgery by US-guided insertion of long needle electrodes (with variable or fixed geometry) into and around the tumor. Up to three metastases not exceeding 3 cm in the diameter were treated with electrochemoterapy. Patients were divided into three groups. In the first two groups were patients with two-stage liver surgery. In the first operation, some of the metastases were treated by electrochemoterapy and removed during the second operations. In the third group patients with unresectable metachronous metastases were treated with electrochemoterapy as the only treatment option.

There was no perioperative mortality. Three patients required reoperation after electrochemoterapy; two because of colon perforation and one because of obstruction of small bowel because of adhesions. None of these complications were related to electrochemoterapy. During or after electrochemoterapy no major heart rhythm changes or myocardial ischemia were found.

Radiological complete response was observed in 85% of treated metastases and partial in 15% after the first radiological evaluation. At the second evaluation, at a median of 147 days after electrochemoterapy, 71% of metastases were still in complete response. Response to electrochemoterapy was the same in metastases located close to major hepatic vessels and metastases away from the vessels. On pathological analysis, non treated metastases had a significantly higher percentage of residual viable tumor compared to electrochemoterapy treated.

We found regressive changes in the whole electrochemoterapy-treated area of the liver with disruption of vessels less than 5 mm in diameter and preservation of the larger vessels and biliary ducts.

Electrochemoterapy of liver metastases is feasible, efficient and safe treatment modality, especially for the metastases in the vicinity of major hepatic vessels.

EXPERIENCE IN TREATMENT OF HEPATOCELLULAR CARCINOMA

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Abstract: *Electrochemotherapy provides non-thermal ablation of cutaneous as well as deep seated tumors. Based on positive results of the treatment of colorectal liver metastases, we conducted a prospective pilot study on hepatocellular carcinomas with the aim of testing the feasibility, safety and effectiveness of electrochemotherapy. Electrochemotherapy with bleomycin was performed on 17 hepatocellular carcinomas in 10 patients using a previously established protocol. The procedure was performed during open surgery and the patients were followed for median 30 months. Electrochemotherapy was feasible for all 17 lesions, and no treatment-related adverse events or major post-operative complications were observed. The median size of the treated lesions was 24 mm (range 8-41 mm), located either centrally, i.e., near the major hepatic vessels, or peripherally. At last radiological follow-up the complete response rate was 90% per patient (9/10) and 94% per treated lesion (16/17). Electrochemotherapy of hepatocellular carcinoma proved to be a feasible and safe treatment in all 10 patients included in this study. To evaluate the effectiveness of this method, longer observation period is needed; however, the results at medium observation time of 30 months after treatment are encouraging, in 16 out of 17 lesions complete response was obtained. Electrochemotherapy is predominantly applicable in patients with impaired liver function due to liver cirrhosis and/or with lesions where a high-risk operation is needed to achieve curative intent, given the intra/perioperative risk for high morbidity and mortality.*

INTRODUCTION

Hepatocellular carcinoma (HCC), together with intrahepatic cholangiocarcinoma, represents more than 98.5% of all primary liver tumors, and its incidence is rising worldwide. HCC is the third most common cause of cancer-related deaths in the world and is responsible for between 650,000 and one million deaths globally per year (1-3).

The optimal treatment options for patients with HCC are curative surgical resection, liver transplantation and, in rare cases, radio-frequency ablation (RFA). Other methods, such as local ablative techniques (percutaneous ethanol (PEI) or acetic acid injection (PAI) in tumor, RFA, microwave ablation (MWA), transarterial chemoembolization (TACE), targeted therapy, chemo- and radiotherapy and others are used only as palliative treatment and in some cases as bridging therapy (TACE, RFA) for possible curative liver transplantation. Most patients with HCC are complex, with only 20% having straight forward treatment scenarios. Therefore, the majority of patients (more than 60%) receive some combination of therapies, depending on the stage of the disease (4-10).

Despite intensive surveillance programs, considerable recent therapeutic advances, and the use of potentially radical treatments, prognosis and life expectancy remain low in patients with HCC (11). Electroporation-based treatments, including irreversible electroporation (IRE) and electrochemotherapy, are new local treatment approaches that are gaining importance. Electrochemotherapy already has an established place among other local treatments for the treatment of cutaneous tumors (12), but the translation of electrochemotherapy into deep-seeded

tumors is lagging behind (13).

However, the first encouraging results for the treatment of colorectal liver metastases have already been published (14,15). Based on the encouraging clinical results, we conducted a prospective pilot clinical study to establish the feasibility, safety, and effectiveness of electrochemotherapy in the treatment of HCC. In the study, patients not amenable to other therapeutic ablative techniques were included. Furthermore, electrochemotherapy was also employed to treat tumors located in the vicinity of the major blood vessels where other ablative techniques, such as RFA or MWA, would not have been efficient due to the heat sink effect.

PATIENTS AND METHODS

Study design

The study was designed as a prospective, pilot study. Patients were presented at the multidisciplinary team meetings consisting of a surgeon, radiologist and gastro-oncologist. Before inclusion into the trial, all patients signed written informed consent. The primary endpoint of the study was to assess the feasibility and safety of electrochemotherapy in the treatment of HCC. The secondary aim was to determine the efficacy of ECT, based on a radiological evaluation of treated lesions, as measured by modified Choi criteria (17). Electrochemotherapy was performed according to the Standard Operating Procedures for treatment of cutaneous tumors and the associated modifications for the treatment of liver tumors and reporting of data according the published recommendations (15,18,19).

Patients

In this trial, 10 patients with 17 lesions were enrolled from February 2014 to November 2016, based on the inclusion and exclusion criteria (Table 1). The diagnosis was confirmed either histologically (in 4 patients) (20), or by typical radiological appearance according to the EASL-EORTC Clinical Practice Guidelines for Management of hepatocellular carcinoma (5). Patients were divided into three groups according to the indications and previous treatments.

The first group represented patients in whom the local ablative technique was unsuccessful (TACE/RFA) and electrochemotherapy was offered as an additional treatment. In this group, 3 patients with 6 lesions were treated. Two of these patients underwent TACE, which was unsuccessful (progress of the treated lesion at the follow up), and further treatment with TACE was not indicated. According to the Barcelona Clinic Liver Cancer (BCLC) algorithm (21), treatment for advanced or terminal stage disease should be offered. The third patient in this group had previously been treated with RFA, which was unsuccessful, and other ablative techniques were not indicated.

The second group included patients for whom transplantation, radical surgery or other local ablative techniques were not indicated due to patients' performance status, the location of the lesions, or contraindications to the ablative techniques. However, electrochemotherapy was performed with curative intent. In this group, 6 patients with 9 lesions were treated.

The third group included a patient for whom electrochemotherapy was offered as “bridging” to transplantation option. In this patient, 2 lesions were treated. During the first procedure in 2009, right hemihepatectomy with resection of middle and right hepatic veins in un-cirrhotic liver was performed due to HCC. In 2015, the patient developed 2 new HCC lesions located in proximity to the left hepatic vein, so electrochemotherapy was offered to the patient as a “bridging” to liver transplantation.

Lesions were defined as “central” or “peripheral” based on their relation to the major blood vessels. The term “central” was used for the lesions in the close vicinity

of the major blood vessels including the main hepatic or portal veins and the main hepatic arterial branches. The term "peripheral" was used for lesions not adjacent to the major blood vessels where RFA or other ablative techniques were not indicated by interventional radiologist blinded to the study (22,23).

Treatment procedure

All 10 patients enrolled in the study were treated during open surgery. Median laparotomy, extended to the right subcostal incision, was performed in 8/10 patients. In 2 patients, only upper median laparotomy was used. The electrodes used for electric pulse delivery were either single long (20 cm) needle electrodes (variable geometry) with 3 or 4 cm active part or 7-needle electrodes fixed on the holder in hexagonal geometry and 3 cm active part (24,25). The choice of electrode use was dependent on the location of the lesion. Electrodes with variable geometry i.e., long needle electrodes were used for deep seated tumors located more than 3 cm below the surface of the liver. The hexagonal electrodes were used for more superficial tumors that had their deepest margins less than 3 cm from the liver surface (24,25). Specifically, the treatment of lesions in segment 8 included the use of both types of the electrodes, where for the use of hexagonal electrodes mobilization of the liver was required. The intraoperative ultrasound was used to identify lesions and aid the positioning of the electrodes into and around the tumor. The long needle electrodes were positioned according to the pretreatment plan prepared for each patient and specific tumor individually using previously developed procedures (26,27). Plans were developed based on computed tomography and/or magnetic resonance scans taken less than 30 days prior to treatment. Target lesions (up to 41 mm in the largest diameter) were segmented. A gradient-based optimization algorithm was used to optimize voltage between each electrode pair to maximize tumor coverage above the reversible electroporation threshold (400 V/cm) and minimize the volume of healthy liver parenchyma above the irreversible electroporation threshold (700 V/cm). The intravenous bolus of bleomycin was given to the patient after the intra-operative ultrasound confirmed the correct electrode placement. Trains of eight electric pulses (electrodes with variable geometry) or 24 (fixed geometry) electric pulses (each pulse 100 ms long) were delivered to each pair of electrodes consecutively. Electric pulses were delivered by electric pulse generator during an interval of 8-28 min after the intravenous injection of bleomycin 15,000 IU/m^2 in bolus, as being determined to be the optimal pharmacological peak for the bleomycin in the tumors (16).

Efficacy assessment based on radiology

Lesions treated in the study were assessed before electrochemotherapy by contrast-enhanced computed tomography (CECT) or with magnetic resonance imaging (CEMRI) using a distinct hepatocyte contrast (gadoliniumethoxybenzyl-diethylenetriaminepentaacetic acid-Gd-EOB-DTPA). The follow-up was performed by CECT in all the patients but one in whom the CEMRI was performed at the 3- months follow-up. Images were evaluated by two radiologists, one of whom was blinded to the trial. Modified Choi criteria were used to assess the treatment response (17). Evaluations of both radiologists were in complete consensus.

RESULTS

Feasibility, safety, and response to treatment evaluation were evaluated for all 10 patients and 17 lesions.

Feasibility

Electrochemotherapy was feasible in all 10 patients enrolled in the study, according to the inclusion and exclusion criteria (Table 1). Three females and 7 males were included, with a median age 69.5 years

Table 1 Inclusion and exclusion criteria for electrochemotherapy in HCC.

Inclusion criteria
1. HCC confirmed by radiological imaging and/or histology.
2. Age more than 18 years.
3. Life expectancy more than 3 months.
4. Performance status Karnofsky 70 or WHO (World Health Organization) < 2.
5. Signed informed consent.
6. Unanimous decision of the multidisciplinary liver tumor team before entering the trial (surgeon, gastro-oncologist and radiologist).
Exclusion criteria
1. Multiple primary tumors.
2. Extrahepatic disease.
3. Poor performance status.
4. Clinically significant ascites.
5. Exposure to cumulative bleomycin doses in excess of 400 mg.
6. Allergic reaction to bleomycin.
7. Impaired kidney function (Creatinine > 150 mmol/l).
8. Pregnancy, epilepsy, heart arrhythmias or patient having cardiac pace maker.

(range: 57-78 years). Three patients had undergone previous treatment with TACE and/or RFA, and one had undergone liver resection. Six patients had received electrochemotherapy as a primary treatment. The previously operated patient had electrochemotherapy as a bridging procedure for liver transplantation.

Patients were treated according to the Standard Operating Procedures for cutaneous tumors, modified for the liver tumors during open surgery (16,24). The median size of the treated lesions was 24 mm with a range of 8-41 mm. Electrochemotherapy was also feasible in patients with centrally located lesions in the vicinity of major hepatic vessels (8/17 lesions).

Safety

Adverse reactions related to electro-chemotherapy did not occur, despite the American Society of Anesthesiologists (ASA) score of 3 (8/10 patients) and ASA score of 2 (2/10 patients). No intraoperative or postoperative complications during the first 24 h occurred. The exceptions were the two patients with the ascites production after the procedure due to transient liver failure. Ascites was resolved by conservative measures. Nevertheless, patients were classified as Clavien-Dindo 3a and 3b because in both additional diagnostic/intervention was necessary: in one patient the ERCP was performed due to choledocholithiasis; the second patient had elevation of cholestatic enzymes and the endoscopic ultrasound was performed to clarify the origin of elevated enzymes. The impaired liver function was a result of liver cirrhosis before the operation and was not related to the electrochemotherapy.

All 10 patients were discharged from the hospital after a median hospitalization of 5.5 days (range: 2-20 days) and were followed on an outpatient basis. ECG signals were recorded during and 24 h after the electrochemotherapy. No onset of new or worsening of existing pathological morphological changes was recorded. There were no signs of myocardial ischemia, new-onset of atrial and/or ventricular extrasystoles, or increased frequency of abnormal heartbeats in

relation to the electrochemotherapy procedure. Centrally located tumor lesions (8/17) near major hepatic vessels were successfully treated without adverse events.

Effectiveness

The first radiologic follow-up was 1 month after treatment (median 31 days; range from 23 to 45 days). All 17 lesions were evaluated and a complete response was found in 15/17 lesions (88%). Two lesions had a partial response according to the modified Choi criteria, due to the small field of enhancement, without changes in lesion size.

The second radiological follow-up was 3-6 months after the treatment (median 194 days; range from 100 to 218 days). All 17 lesions were evaluated, and according to the modified Choi criteria, all of the lesions that had been initially evaluated after 1 month, i.e., the 15/17 lesions, remained in complete response. Two lesions identified in the previous follow-up as partial responses (2/17, 12%) remained in the stage of partial response and the patients were considered being in stable disease.

The last radiological follow-up was 12-37 months after the treatment (median 30 months). One of the lesion that was previously evaluated as stable disease, was described as complete response after last radiological follow-up. The rest of the lesions remained unchanged, therefore a complete response was observed in 16/17 lesions (94%).

DISCUSSION

Electrochemotherapy has, after successful translation into treatment of cutaneous tumors, progressed into translation of deep seated tumors. This study confirmed the feasibility, safety and effectiveness of electrochemotherapy in the treatment of HCC. No treatment or postoperative adverse events were recorded, including in patients with lesions located near the major hepatic vessels. The overall response was high, 94% (16/17) of the treated lesions and 90% (9/10) of patients had complete responses.

The feasibility and safety of electrochemotherapy was already demonstrated in a previous study on the treatment of colorectal liver metastases. The response rate of that study was 85% complete responses on 29 metastases in 16 patients which is comparable to the 94% complete response rate in this prospective pilot study on HCC (15). The technology that has proven to be feasible and safe in the previous study was also confirmed in this study and another recently published study (14), in cases where other ablative techniques are not indicated.

In this study, not only patients with previously unsuccessfully treated tumors, but also patients for whom standard treatment with curative intent could not be offered were included. In one patient, this method was used as a bridging to liver transplantation. Two patients had post-operative complications in the form of transient liver function failure with consequent ascites production. Based on poor performance status of the recruited patients in whom other treatments were not feasible, electrochemotherapy provides effective treatment of lesions in such patients. Therefore, it could be considered as a technique with curative intent, which, however, needs to be confirmed in a phase II study in a larger cohort of patients.

One of the limitations of this approach is that larger tumors tend to have lower response rates. As indicated by several other studies, tumors larger than 3 cm in diameter seldom have complete responses (28,29). The method in our case was upgraded by the treatment plan that intended to predict the optimal electrode placement for effective electroporation of the tumors. This certainly aided better execution of the electroporation of lesions larger than 3 cm in diameter, but the step for effective verification of

the tumor coverage after electroporation is still missing. This can be executed either by US verification, as noted in IRE and also by electrochemotherapy, or by development of measuring tools for the current distribution in the tumors by MRI, which is still in progress (29-31).

This study, however, has some limitations. Based on the fact that it is a pilot study and on small cohort of patients, only ten, the conclusion about the effectiveness of electrochemotherapy is premature. Nevertheless, the preliminary data foster the continuation of this study in phase II one.

In conclusion, our experience demonstrate feasibility, safety and provides preliminary data on the high effectiveness of electrochemotherapy in HCC. Electrochemotherapy could be predominantly applicable in patients with impaired liver function due to liver cirrhosis and/or with lesions where a high-risk operation is needed to achieve curative intent.

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