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Electrochemotherapy of cholangiocellular carcinoma at hepatic hilum: A feasibility study

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ABSTRACT

Aim: We evaluated feasibility, safety and efficacy of Electrochemotherapy (ECT) in a prospective series of patients with unresectable Perihilar-Cholangiocarcinoma (PHCCA).

Patients and methods: Five patients with PHCCA underwent ECT. Three patients underwent percutaneous ECT of a single PHCCA nodule. One patient underwent resection of a nodule in the IV segment and intraoperative ECT of a large PHCCA in the VIII segment. Another patient underwent percutaneous ECT of a large PHCCA recurrence after left lobectomy and RF ablation of a synchronous metastasis in the VI segment.

ECT was performed under US guidance. Efficacy was evaluated by contrast-enhanced multiple-detector-computed-tomography (MDCT) 4 weeks after treatment. Follow-up entailed MDCT every 6 months thereafter.

Results: No major complication occurred. Follow-up ranges from 10 to 30 months. Four weeks post-treatment CT showed complete response in 3 cases. These patients are still alive, and follow-up CT controls demonstrated no local or distant intrahepatic recurrences and no biliary duct dilation in 2 cases and local recurrence at 18 months follow-up control in 1 patient. In the remaining 2 cases, 4-weeks-post-treatment CT showed incomplete response (>90%). In these patients follow-up CT demonstrated local progression of the disease at 6 months. One of them had bilateral external biliary drainages and died because of tumor progression at 16-months-follow-up. The other patient, died at 10 months follow-up for cardiovascular failure not related to the hepatobiliary disease.

Conclusions: ECT is feasible, safe and effective therapy to improve prognosis and quality of life of patients with unresectable PHCCA.

Introduction

Cholangiocarcinoma (CCA) represents less than 2% of all human neoplasms and is the second most common primary hepatic malignancy after hepatocellular carcinoma, accounting for 10–15% of liver malignancies [1]. Anatomical classification, that also correlates with prognosis, entails: a) intrahepatic CCA (ICCA); b) perihilar CCA (PHCCA), located within 2 cm from the bifurcation of the common bile duct; c) distal CCA. PHCCA also called Klatskin tumor, represents 46%–97% of all bile duct cancers [2] and is an aggressive and silent tumor, with non-specific symptoms until advanced stages, leading in most cases to a late diagnosis of an unresectable tumor with poor prognosis [3]. The 5-year survival of overall untreated CCAs ranges from 0 to 10%. Patients with unresectable PHCCA at diagnosis have a median survival of 6 months [4–6]. Surgery represents the only chance of long-term survival and cure of PHCCA. However, the 5-year survival, even in case of tumor-free margins of the resected specimen (R0 resection), is in the range of 20–40% [6].

Chemotherapy results for advanced PHCCA is rather disappointing. Regimen with gemcitabine and cisplatin, the current standard

Abbrevations: CCA, Cholangiocarcinoma; ICCA, Intrahepatic Cholangiocarcinoma; PHCCA, Perihilar Cholangiocarcinoma; ECT, Electrochemotherapy; EP, Electroporation; MDCT, multiple detector computed tomography; CT, Computed Tomography; US, Ultra sound; TACE, Transarterial chemoembolization; RF, Radiofrequency ablation; MW, Microwave ablation; ICSP, Intraductal chilled saline perfusion; IRE, Irreversible electroparation.

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palliative treatment, only prolongs overall survival of patients with PHCCA by a few months [7]. Locoregional therapies do not represent a curative option alternative to surgery in the treatment of CCA. Transarterial chemoembolization (TACE) and Radioembolization did not demonstrate any efficacy in PHCCA patients [8]. Photodynamic therapy [9], endoscopic intraluminal Radiofrequency ablation (RF) [10], external radiotherapy or Intraluminal brachytherapy with Ir-S192 [11,12] demonstrated a possible role as palliative treatments, with no substantial improvement of survival of patients. Percutaneous or intraoperative thermal ablation of the tumor mass by RF or Microwawe (MW), are contraindicated because of possible severe thermal injury of main bile ducts, hepatic hilum vessels or duodenum [13,14].

A potential ideal ablation technique for PHCCA should be able to kill tumor cells at hepatic hilum, without heat generation in order to avoid any damage to bile ducts, arterial vessels and to portal vein walls. Electrochemotherapy (ECT) is a non-thermal local tumor ablation modality using Electroporation (EP) [15,16] to enhance cell membrane permeability, and enable non-permeant or poorly permeant chemotherapeutic agents to enter cells, greatly increasing their efficacy [17,18]. Local application of electric pulses to the tumor increases drug delivery into cells, specifically at the site of electric pulse application (Fig. 1). Drug uptake by delivery of electric pulses is increased only for those chemotherapeutic drugs whose transport through the plasma membrane is impeded [17]. Among many drugs tested during preclinical development, bleomycin and cisplatin demonstrated high activity when combine with EP and entered clinical use [18,19]. Safety and efficacy of the use of ECT in proximity of vascular and ductile structures of liver and pancreas have been already demonstrated in several studies [15,16]. Effective and safe treatment of tumor thrombus in portal vessels at hepatic hilum has been recently reported [20].

In order to evaluate the feasibility, safety and efficay of the procedure, we present a prospective case series of patients with unresectable PHCCA treated with ECT.

Patients and methods

The present study, “ECT treatment of PHCCA: a feasibility study”, was approved by the Institutional Board of our Institute and was conducted according to the declaration of Helsinki.

Selection criteria for ECT treatment

Patients must have a diagnosis of PHCCA considered unresectable according to one or more of the following criteria: (1) Infiltration of both left and right main biliary ducts; (2) Malignant Portal vein thrombosis of the right and/or left portal branch and/or of the main portal vein; (3) tumor located next to the confluence of the main biliary ducts at hepatic hilum. Nodules abutting the duodenum, stomach, transverse colon or gall-bladder were not considered exclusion criteria. Patients were considered eligible for ECT intervention if the following condition were present: (1) Karnofsky performance status > 70; (2) normal liver and renal functions; (3) platelet count > 60.000/mm^3, INR < 1.5; (4) total bilirubin <4 mg/dL before or after biliary drainage; (5) absence of ascites at the time of treatment; (6) patient's consensus to undergo the procedure.

Causes for exclusion from the treatment were: (1) extrahepatic CCA metastases; (2) heart impairment, arrythmias or presence of a cardiac pace-maker; (3) severe lung or renal or hepatic insufficiency; (4) epilepsy; (5) allergy to bleomycin.

Case series

From May 2015 to May 2016, 32 patients with PHCCA were observed at our Unit of Interventional Hepatology in a tertiary care Institution—“A.Tortora” Cancer Hospital. Five patients (4 M, 1F; mean age 67–82year) with PHCCA (diameter: 3.0–6.0 cm, mean = 4.2 cm) fulfilled the inclusion criteria and underwent ECT. All patients had a perihilar Cholangiocarcinoma considered inoperable from a multidisciplinary team (Surgeon, Oncologist, Hepatologist, Radiologist). Than, two out of the five patients also had a peripheral Cholangiocarcinoma as a second nodule (IV and VI segment respectively).

For the diagnosis of PHCCA, all patients underwent US guided percutaneous biopsy of the tumor with an 18 gauge-cutting needle (Biomol, HS Hospital service, Rome, Italy) before ECT procedure. Two patients had a large post-surgical recurrence, 3 were observed as first diagnosis. Two patients had a Bismuth-corlette-4-CCA, and 3 patients showed infiltration of the hepatic hilum and/or inferior vena cava (IVC) without intrahepatic biliary duct dilation.

All patients provided written informed consent to receive ECT treatment. After the informed consent, two out of five patients, 79 and 82 years old, refused chemotherapy. The other three patients presented with intrahepatic recurrence (two cases) or local post-surgical disease progression while on standard systemic chemotherapy with gencitabine plus oxaliplatin.

Before ECT procedure, all patients underwent: (1) serum blood tests for liver function and haemocoagulation and serum tumor

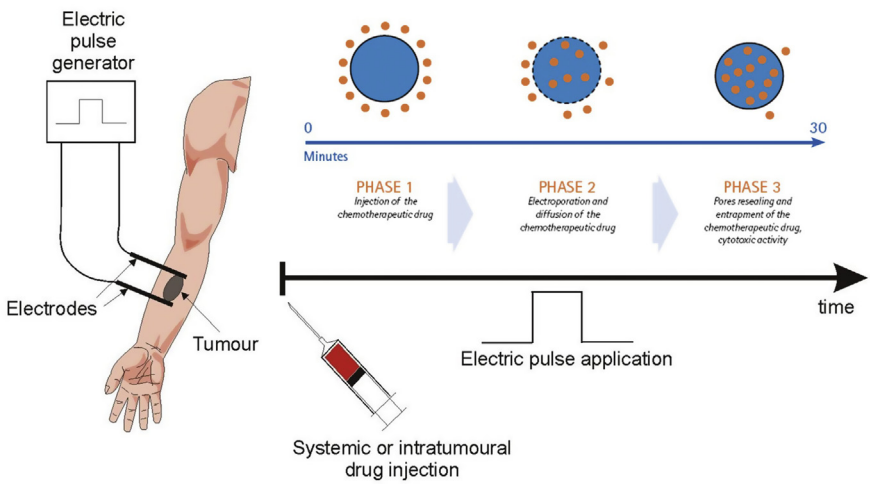

Fig. 1. Electrochemotherapy technique: Electroporation enhances cells' membrane permeability, and enables poorly permeant chemotherapeutic agents to enter cells. In combination with tumor cells Electroporation, intracellular concentration and therefore cytotoxicity of bleomycin increases 300- to 700-folds.

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