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Original Research

Safety and feasibility of electrochemotherapy in patients with unresectable colorectal liver metastases: A pilot study

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HIGHLIGHTS

- Electrochemotherapy is a novel ablation technique combining chemotherapeutic agents with reversible cell membrane electroporation.
- Its application for deep-seated malignancies is under investigation.
- We present the results of a prospective, pilot study to evaluate the feasibility, safety, and efficacy of intraoperative electrochemotherapy combined with open liver surgery for otherwise unresectable colorectal liver metastases.
- A total of 9 colorectal liver metastases were treated in 5 patients with 20 electrode applications. No intraoperative complications were observed. At day 30, complete response was 55.5% and stable disease 45.5%. The 6-month overall and progression-free survival was 100% and 80%, respectively.
- Larger studies and longer follow-ups are favored to better define its role in the treatment of secondary liver malignancies.

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ABSTRACT

Background and objectives: Electrochemotherapy is a novel ablation technique combining chemotherapeutic agents with reversible cell membrane electroporation. Previous experiences have shown its efficacy for cutaneous tumors. Its application for deep-seated malignancies is under investigation. We performed a prospective, pilot study to evaluate the feasibility, safety, and efficacy of intraoperative electrochemotherapy for otherwise unresectable colorectal liver metastases.

Methods: Electrochemotherapy with bleomycin was combined with open liver resection and performed with linear or hexagonal needle electrodes according to an individualized pretreatment plan. The primary endpoints were: feasibility, as ratio of completed to planned treatments; safety, and efficacy, as per response assessed at 30 days with MRI and according to RECIST. The secondary endpoint was overall and progression-free survival at month 6.

Results: A total of 9 colorectal liver metastases were treated in 5 patients with 20 electrode applications. No intraoperative complications were observed. At day 30, complete response was 55.5% and stable disease 45.5%. All (5) patients reached a 6 months overall survival, and 4 out of 5 patients had 6 months progression free survival.

Conclusions: Electrochemotherapy is a feasible and safe adjunct to open surgery for treatment of unresectable colorectal liver metastases. Larger studies and longer follow-ups are favored to better define its role in the treatment of secondary liver malignancies.

1. Introduction

Colorectal liver metastases (CLM) are a significant cause of morbidity and mortality [1]. Up to 25% of patients with colorectal carcinoma have metastases at diagnosis, and 40–50% develop metastases during the follow up with a 5-year survival rate

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between 5% and 30% [1]. Surgical resection is still the gold standard for treatment of CLM, and radical surgery provides favorable survival rates at 3 and 5 years and allows for cure in as much as 20% of patients [1]. However, only 10–20% of patients are eligible to resection at the time of diagnosis [1]. Recently, a number of conversion approaches for patients with liver-only or liver-dominant, unresectable metastases were reported, and introduction of neoadjuvant combination schedules has allowed to increase resectability rates to 20–35% [2].

Conversion schedules for unresectable CLM usually include chemotherapy agents tailored to histology of the primary tumor and profiling of cell receptors involved in tumor growth and control. Use of cetuximab and bevacizumab - monoclonal antibodies to the epidermal growth factor (EGFR) receptor and vascular endothelial growth factor receptor, respectively - in combination with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or irinothecan (FOLFIRI)-based regimens has increased the objective response rate to an average of 68% vs. 57%, with resulting 38% conversion rate as opposed to 30% [2,3]. A recent randomized, phase-3 study has shown that the EGFR-specific monoclonal antibody panitumumab in combination with FOLFOX improves progression-free survival vs. FOLFOX alone from 8.0 to 9.6 months [3]. However, mutations of the Kirsten rat sarcoma viral oncogene homologs (KRAS), which are present in approximately 40–50% of individuals, reduce the effectiveness of these schedules, thus limiting the possibility of conversion to surgical resection for a number of eligible patients [4].

Combination of surgery and radiology-assisted procedures – such as radiothermal ablation, cryoablation, irreversible electroporation, and portal embolization – may be offered to patients with initially unresectable CLM in view of attaining radicality, tumor debulking or limiting tumor progression [5]. However, the feasibility rates of these combined approaches may be reduced for patients with bilobar involvement or previous liver surgery [5].

Electrochemotherapy (ECT) is a non-thermal technique that combines poorly or non-permeant chemotherapeutic drugs, such as bleomycin or cisplatin, in association with cell membrane electroporation. This latter consists of local application of short, high-voltage pulses to cells or biological tissue and facilitating intracellular diffusion of hydrophilic drugs [6,7]. Among a number of different drugs, bleomycin shows the highest cytotoxicity rates when coupled to cell membrane electroporation (up to 1000-fold) [8]. In turn, this allows reducing drug dosages and related side effects and improving patients' quality of life.

Previously, the international, multicenter clinical study ESOPE (European Standard Operating Procedures for Electrochemotherapy) developed the Standards of Operating Procedures (SOPs) for ECT with use of the Cliniporator™ (IGEA S.p.A., Carpi (MO), Italy). Standardization of this procedure has allowed its implementation in over 140 cancer centers in Europe and has contributed to its diffusion in clinical practice [9,10].

The efficacy of ECT for treatment of a number of solid tumors and skin malignancies has already been reported in previous clinical studies [11]. Its use is currently standardized for treatment of cutaneous and subcutaneous lesions, regardless of their histology [11]. Application of ECT for internal tumors is currently under evaluation [12–16]. A recent pilot study [17] performed on 16 patients with unresectable liver metastases has proved the safety and efficacy of ECT in this setting, confirming previous reports about the advantages of ECT vs. Thermal ablation for multiple lesions located in proximity to intrahepatic vascular structures, bile ducts or viscera [18,19]. We present herein the results of a prospective, pilot, single-center study to assess the feasibility, safety, and efficacy of ECT in combination with liver resection for treatment of otherwise unresectable CLM.

2. Materials and methods

2.1. Study design

This was a 30-day with a 6-month (M)-extension, prospective, pilot, single-arm, open-label, single-center study on patients with unresectable CLM and carried out at the Hepatobiliary surgery and Liver transplantation Unit of University of Pisa Medical School Hospital. The study (NCT ID # 02709811) was conducted in accordance with the Standards of Good Clinical Practice (GCP) of the European Union and the current revision of the Declaration of Helsinki. The local ethics committee approved the trial.

2.2. Patients

Patients were included if: 1) consenting; 2) adult (≥18 years); 3) had an Eastern Cooperative Oncology Group (ECOG) score ≤2; 4) with life expectancy ≥6 months; 5) affected with histology-proven, metachronous or synchronous CLM not amenable to curative resection, and 6) off chemotherapy for >30 days before ECT. Target tumor lesions to be treated with ECT were: 1) ≤3 cm. 2) previously untreated by surgery or radiology-guided procedures; 3) not otherwise amenable to resection, due to size, number, location, proximity to vascular/biliary structures or extent of parenchymal resection, and 4) located within 2 cm from the liver capsule.

Patients were excluded if: 1) >80 years; 2) pregnant or breast-feeding; 3) affected with any disease that precluded surgery at investigator's discretion (e.g. serious infections, severe myocardial disease, lung disease, liver function decompensation, or other systemic conditions); 4) with acute or chronic renal insufficiency (as per an estimated glomerular filtration rate <30 mL/min according to the 4-item modified renal and disease formula); 5) had known hypersensitivity to bleomycin; 6) were on chronic treatment with anticoagulants; 7) had contraindications to 3-T Magnetic Resonance Imaging (MRI) (e.g. pacemakers holders and patients with non compatible metal devices).

2.3. Treatment

Treatment was performed in the operating room on patients undergoing planned surgical resection (in the form of anatomical or wedge resection(s)). Patients were treated under general anesthesia and oro-tracheal intubation. After induction of anesthesia, the patient was prepared and draped for surgery. Once the liver resection was completed, ECT was started and used for residual tumor lesions not otherwise amenable to surgery as per number, location, and proximity with vascular and/or biliary structures or extent of parenchymal resection. According to the ESOPE Standard Operating Procedures (SOPs), bleomycin was administered by i.v. bolus in 30–60 s at a dosage of 15,000 IU/m^2. The Cliniporator™ (Igea S.p.A, Carpi (MO), Italy) was activated 8 min after the end of i.v. injection, and the lesions were treated within 28 min to achieve maximal drug concentration in the target lesion [20]. Needle electrodes with a linear or hexagonal configuration (L or H-40-IN) were used to deliver the electric pulses according to the size and location of the target lesions (≤3 cm). These electrodes are 4 cm long; have a 2-cm insulated tip sheathed in polyethylene terephthalate, and a 2-cm active shaft. The electric pulses were delivered as follows: 96 pulses of 730 V/cm and 100μs duration at a 5000-Hz frequency [10]. The electric pulses were synchronized with the ECG using the R-wave detector Accusync 42 (AccuSync Medical Research Corporation, CT, USA).

With the aid of ultrasound guide, the surgeon could perform multiple insertions of the electrodes in the tumor to achieve a treatment area equal to the target lesion with a 3–5 mm margin of