International Journal of Surgery 18 (2015) 230–236

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Electrochemotherapy in locally advanced pancreatic cancer: Preliminary results

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HIGHLIGHTS

- Electrochemoterapy can treat patients with locally advanced pancreatic adenocarcinoma.
- We have recordered no side effects or major complications with good functional result.
- No damage to surrounding viscera that required medical or surgical treatment.

ARTICLE INFO

Article history:
Received 11 March 2015
Accepted 22 April 2015
Available online 24 April 2015

Keywords:
Electrochemotherapy
Pancreatic adenocarcinoma
Safety
Treatment assessment

ABSTRACT

Objective: Report the preliminary results on electrochemotherapy (ECT) in the treatment of locally advanced pancreatic cancer of a phase I/II study and described the new functional imaging tools to assess ECT response in Magnetic Resonance (MR) imaging compared to morphological Computer Tomography (CT), ultrasound (US) without and with contrast enhancement (CEUS) and MR Imaging.

Materials and methods: Thirteen patients were enrolled in an ongoing clinical phase I/II study approved by Ethical Committee of National Cancer Institute G. Pascale Foundation – IRCCS of Naples. ECT with bleomycin was performed during open surgery. All patients underwent US and CT scan, before and after ECT treatment; 7 patients were evaluated using morphological and functional (dynamic contrast enhancement-DCE and diffusion weighted- DW) parameters in MR; 5 patients underwent CEUS. RECIST criteria were used to evaluate ECT response on US, CT and MR images. Functional parameters were also used to evaluate ECT response on MR images.

Results: No acute (intraoperative) and/or postoperative serious adverse events related to electrochemotherapy were observed; no clinically significant electrocardiographic, hemodynamic, or serum biologic changes were noted. No clinically relevant elevation of amylase or lipase levels was observed and no bleeding or damage to surrounding viscera occurred. In three patients had seen splenic infarction without thrombosis of the splenic vessels.

Conclusion: Electrochemotherapy is feasible and safe treatment modality in patients with locally advanced pancreatic adenocarcinoma. Dynamic and diffusion MR imaging in comparison to MR morphological sequence alone and to UC and CT imaging is more suitable to assess ECT treatment response. CEUS is not indicated in follow up after ECT.

1. Introduction

Pancreatic adenocarcinoma is one of the most aggressive forms of cancer, with an increasing global incidence of nearly 340000 in 2012. Surgical resection offers the only chance for cure, but only 20 per cent of patients present with resectable disease. At presentation, about 40 per cent of patients with pancreatic cancer are diagnosed with metastatic disease (stage IV) and the remaining 40 per cent are diagnosed with locally advanced pancreatic cancer (LAPC). LAPC is defined as non-metastasized but unresectable disease due to involvement of the coeliac trunk or superior mesenteric artery (stage III disease) [1]. LAPC is associated with a very poor prognosis, and current standard therapy is limited to chemotherapy or chemoradiotherapy. Gemcitabine is the most commonly used chemotherapy agent in pancreatic cancer, however recent studies have shown that in combination with other chemotherapy agent's

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http://dx.doi.org/10.1016/j.ijsu.2015.04.055
1743-9191/

further improvements in overall survival can be gained [2–4]. Only a limited groups of patients response to chemotherapy, so tumour debulking or interstitial ablation has been investigated as a potential additional therapy [5–8]. Changes in cell membrane permeability owing to an induced electric field was first described in the 1970s and termed electroporation. Electroporation can be applied in either an irreversible [9–11], as a direct ablation modality, or a reversible manner [12–15], as a physical delivery system, depending on the strength and duration of the electrical field. Reversible electroporation has been used to promote uptake of chemotherapy into tumor cells—Electrochemotherapy (ECT) [15]. ECT is based on the electroporation of cells in tissues and the concomitant administration of low doses of non-permeant or poorly permeant chemotherapeutic drugs. The application of an external electrical field to a cell membrane induces a transient and reversible orientation of its polar molecules, with an increased permeability [12–15]. This transient permeability may allow the cell to a more high dose of chemotherapeutic drugs, that in absence of this transient permeability would not occur, with increases the cytotoxic effects of the chemotherapeutic drugs. This local potentiation of chemotherapy allows to reduce the doses of the drugs, lowering the side effects and increasing the efficacy of chemotherapy [12–15]. Electrochemotherapy with bleomycin has been shown to be very effective in different cutaneous and subcutaneous tumors such as melanoma and chest wall breast cancer recurrence [16,17] or for the treatment of squamous cell carcinoma of the head and neck when compared with bleomycin therapy alone [18,19].

Translation of electrochemotherapy into treatment of deep-seated tumors is being currently explored with the introduction of technological advancements for efficient electroporation-based treatment of internal tumors [20,21]. ECT in pancreatic cancer has been investigated by Jaroszeski et al. in a preclinical trial using an animal model [22].

The purpose of our single center is to report the preliminary results on electrochemotherapy in treatment of locally advanced pancreatic cancer of a phase I/II study based on the treatment parameters of the previous ESOPE study [23]. According to our previous study [24] we described also the new functional imaging tools to assess the electrochemotherapy response in Magnetic Resonance (MR) imaging compared to morphological Computer Tomography (CT), ultrasound (US) without and with contrast enhancement (CEUS) and MR Imaging.

2. Materials and methods

2.1. Study population

The patients were recruited in a clinical phase I/II study approved by Ethical Committee of National Cancer Institute G. Pascale Foundation – IRCCS of Naples. The study endpoints were the feasibility and safety of ECT in the multimodal treatment of pancreatic cancer in patients with locally advanced disease and not suitable for radical surgery.

Thirteen patients (6 female and 7 male) from November 2011 to January 2015 were enrolled in this prospective study. Inclusion criteria were: age between 18 and 80 years; good mental health; life expectancy $\geq$3 months; histologically confirmed diagnosis of pancreatic adenocarcinoma; locally advanced disease (stage III) confirmed to preoperative radiological assessment; unfit for curative surgery. Exclusion criteria were: pregnant women, significant heart disease, coagulation disturbances, allergy to bleomycin, lung and kidney dysfunction, implanted defibrillator or pacemaker, concomitant presence of distant metastases.

Patient's characteristics were reported in Table 1. All patients enrolled in this clinical protocol with diagnosis of pancreas locally advanced adenocarcinoma received systemic chemotherapy before ECT treatment. Two chemotherapy regimens were adopted: Gemcitabine + Oxaliplatin (GEMOX) or 5-FU/Leucovorin, Irinotecan, and Oxaliplatin (FOLFIRINOX). GEMOX regime was consisted of 100-minute infusion of Gemcitabine at a dose 1.000 mg/m2 administered on day 1 and a 2-h infusion of Oxaliplatin at a dose of 100 mg/m2 administered on day 2, in according to He et al. [25]. Treatment was repeated every 2 weeks for 3 months. FOLFIRINOX regime was consisted of 2-h intravenous infusion of Oxaliplatin at a dose of 85 mg/m2 immediately followed 2-h intravenous infusion of Leucovorin at a dose of 400 mg/m^2 with the addition, after 30 min, of 90-minute intravenous infusion of Irinotecan at a dose of 180 mg/m^2. This treatment was immediately followed by intravenous bolus of Fluorouracil at a dose of 400 mg/m^2, followed by a continuous intravenous infusion of 2400 mg/m^2 over a 46-h period every 2 weeks [25].

Nine (9/13, 69.2%) patients were subjected to GEMOX and four patients (4/13, 30.7%) were injected with FOLFIRINOX before ECT treatment (mean time between the begin of chemotherapy treatment and ECT was 126 days, range 118–136). The patients with stable disease or partial response after chemotherapy, proven by clinical and radiological examination, were suitable to receive ECT treatment. Four patients had a biliary stent.

2.2. Surgery protocol

Proposal for participation in this trial for patients was discussed by the medical oncologist, radiation oncologist, and surgeon in a multidisciplinary clinic meeting. Patients were informed of their options, of the details of the clinical trial and informed consent was discussed and obtained.

The surgical technique for ECT was performed through an open laparotomy incision preferably through an adequate midline incision to allow for both appropriate staging of the disease and appropriate mobilization of the pancreatic malignancy based on its lesion location and infiltration. For pancreatic head lesions, an extensive Kocher manoeuvre was performed in order to mobilize the duodenum and the head of the pancreas over to the area of local invasion to allow for easier caudal to cranial needle placement. Similar mobilization of the transverse colon were done inferiorly, depending on the degree of infiltration. In this way, the treating surgeon can indeed decide on whether needle electrodes with linear or hexagonal configuration will be placed through the

Table 1
Characteristics of 13 locally advanced pancreatic cancer patients treated with ECT.

Characteristics (n = 13)	
Histotype, %	
Adenocarcinoma	100 (13/13)
Location, %	
Head	53.8 (7/13)
Body/Neck	46.2 (6/13)
Lesion size, cm (range)	
Axial	5.1 (2.2–9.9)
Anterior – posterior	4.7 (2.2–7.8)
Caudal to cranial	2.6 (1.5–5.0)
Jaundice	
Yes	38.5 (5/13)
No	61.5 (8/13)
Venus involvement (SMV or PV), %	
Yes	84.6 (11/13)
No	15.4 (2/13)
Arterial encasement, %	
Yes	53.4 (7/13)
No	46.2 (6/13)