International Journal of Surgery 21 (2015) S78–S82

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Electrochemotherapy as a new approach on pancreatic cancer and on liver metastases

Salvatore Tafuto [a,*], Claudia von Arx [b], Chiara De Divitiis [a], Claire Tracey Maura [a], Raffaele Palaia [c], Vittorio Albino [c], Roberta Fusco [d], Massimo Membrini [a], Antonella Petrillo [d], Vincenza Granata [d], Francesco Izzo [c], on behalf of ENETS Center of Excellence Multidisciplinary Group for Neuroendocrine Tumors in Naples (Italy)

[a] Department of Abdominal Oncology, Division of Medical Oncology, NCI "Fondazione G. Pascale", Naples, Italy
[b] Department of Clinical Medicine and Surgery, University Federico II of Naples, Naples, Italy
[c] Department of Abdominal Oncology, Division of Surgical Oncology, NCI "Fondazione G. Pascale", Naples, Italy
[d] Department of Diagnostic Imaging, NCI of Naples, "Fondazione G. Pascale", Naples, Italy

ARTICLE INFO

Article history:
Received 18 March 2015
Received in revised form
27 March 2015
Accepted 10 April 2015
Available online 27 June 2015

Keywords:
Electrochemotherapy
Pancreatic cancer
Neuroendocrine tumor
Liver metastasis
Electroporation

ABSTRACT

Electrochemotherapy is a local non-thermal treatment for cancer ablation. Currently, many studies and case report have investigated the differences in effectiveness of electrochemotherapy with respect to tumor type, chemotherapeutic drug, and route of drug administration. ESOPE trial validated standard operating procedures [SOP] for ECT using the Cliniporator device and demonstrated that ECT is a simple, highly efficacious, and cost-effective treatment of cutaneous and subcutaneous nodules from different primary tumors for cutaneous or superficial lesions. This review has the purpose to summarize current knowledge about clinical effectiveness of electrochemotherapy and future prospects regarding its use on pancreatic cancer and liver metastasis not only.

1. Introduction

Electrochemotherapy [ECT] is a non-thermal technique for cancer ablation. It is based on the electroporation of tissue cells and the concomitant administration of chemotherapeutic drugs. Electroporation consists in the local application of short high voltage pulses, which reversibly permeabilize the cell membrane. Indeed, the application of an external electrical field to a cell membrane induces a transient and reversible orientation of its polar molecules, which undergo a controlled rearrangement with an increased permeability of the cell membrane. This transient permeability may allow the exposure of the cell to several molecules [1], such as chemotherapeutic drugs, which are highly cytotoxic but poorly permeating. This ECT principle is used in the administration of chemotherapy to cancer patients.

Electrochemotherapy increases the cytotoxic effects of the chemotherapeutic drugs limiting their action to tissues, which are exposed to the electrical pulses. This local potentiation of chemotherapy allows reduction of the cumulative doses of the drugs lowering the side effects and increasing the efficacy of chemotherapy. The chemotherapy drug is usually administered immediately before electroporation, in order to obtain its high concentration around the tumor cells, which will undergo electroporation. This will increase both the uptake and the cytotoxic effect of the drug, which will be entrapped in the cell after the closure of its transient hydrophilic pores.

Since 1988, when the first *in vitro* research was performed [2], many *in vitro* and *in vivo* studies have followed and now the

* Corresponding author. Medical Oncology, Department of Abdominal Oncology National Cancer Institute – "Fondazione G. Pascale", Via M. Semmola, 80131 Naples, Italy.
E-mail addresses: s.tafuto@istitutotumori.na.it (S. Tafuto), claudia.vonarx@gmail.com (C. von Arx), chiaradedivitiis@yahoo.com (C. De Divitiis), mauratraceydebellis@alice.it (C. Tracey Maura), r.palaia@istitutotumori.na.it (R. Palaia), v.albino@istitutotumori.na.it (V. Albino), r.fusco@istitutotumori.na.it (R. Fusco), massimo.membrini@gmail.com (M. Membrini), a.petrillo@istitutotumori.na.it (A. Petrillo), cinzia.granata80@libero.it (V. Granata), f.izzo@istitutotumori.na.it (F. Izzo).

http://dx.doi.org/10.1016/j.ijsu.2015.04.095
1743-9191/

literature is full of studies, as well as clinical trials of cutaneous subcutaneous and deep-seated tumors.

Several authors tested different chemotherapy drugs *in vitro* studies, in order to evaluate their potential use in combination with electroporation [2–5]. Orlowski et al. showed that the cytotoxicity of certain drugs can be potentiated up to 700 times with electroporation of cells *in vitro*, according to the uptake route of the tumor cell for the specific drug. The most significant potentiation of cytotoxicity [700 times] was noted when electroporation was performed after administration of bleomycin. Overall, all the above mentioned studies confirmed that bleomycin cytotoxicity could be potentiated up to 1000 times with electroporation of the cells [2–4,6–9].

Similar results were reported testing electroporation with cisplatin. Sersa et al. showed that electroporation increases the toxicity of cisplatin by 70-fold for melanoma B16 cell *in vitro*, while no potentiation was reported for other cell lines. Similar results were obtained *in vivo* studies. A good antitumoral effect, with no side effects, is obtained using eight electrical pulses [amplitude 1040 V, duration 100 μs, frequency 1 Hz]. The pulses should be delivered 3 min after the intravenous [IV] administration of 4 mg/kg CDDP. Higher doses of CDDP [8 mg/kg] induced complete response [CR] in 14% of cases, when administered before electroporation to melanoma B16 cells *in vitro* [8].

Both bleomycin and cisplatin were tested in animal models with several types of tumors *in vivo*. These studies confirmed the antitumor effectiveness of ECT. Other platinum containing chemotherapeutic drugs, actinomycin D, adriamycin, mitomycina C, 5-FU, and cyclophosphamide showed promising results *in vitro* and *in vivo* studies. However, these drugs were not evaluated in clinical tests [10].

The use of ECT is consolidated in cutaneous diseases as melanoma [11–15], Kaposi's sarcoma [16–18], head and neck tumor [19,20] and in cutaneous metastatis of breast cancer [21]. In fact, in 2006 the European Standard Operating Procedures of Electrochemotherapy [ESOPE] study validated standard operating procedures [SOP] for ECT using the Cliniporator device and demonstrated that ECT is a simple, highly efficacious, and cost-effective treatment of cutaneous and subcutaneous nodules from different primary tumors [22].

This review provides a concise overview of current status of ECT and of its clinical in new areas as liver metastasis from visceral and deep-seated tumoral and in pancreatic cancer.

2. ECT as new approach on pancreatic cancer

To date, only few patients with pancreatic cancer benefit from current standard therapies. Therefore, there is the need to investigate and experiment new techniques and therapeutic modalities to improve the chances of curing patients with pancreatic cancer. ECT should offer the possibility of treating tumors close to the main pancreatic duct, peri-pancreatic vessels, duodenum, stomach and peritoneum thanks to the fact that this technique has no thermal effects.

ECT has been recently investigated by Jaroszeski et al. who conducted a preclinical trial using an animal model [23]. Pancreatic cancer was induced in hamsters, which then underwent ECT consisting in IV bolus of bleomycin or doxorubicin followed by the application of electrical pulses to the diseased pancreas. The authors reported a CR rate of 25% when ECT was performed using bleomycin, which showed to be superior to doxorubicin.

Electrochemotherapy seems to be safe when used for treating experimental pancreatic cancer, as demonstrated by another preclinical trial, which was conducted at the Orthopedic Institute Rizzoli in Bologna, Italy [data unpublished]. Nine rabbits underwent ECT before being terminated for autopsy at 24 h [#2], 72 h [#2], 15 days [#2], and 30 days [#3]. The rabbits were closely monitored after ECT and no deficit [anorexia] of their general status and/or complications [pancreatitis, intestinal obstruction, fistulas, or bleeding] of the therapy were recorded. At autopsy, the pancreas was removed from the animal and examined by the pathologist who found no necrosis or inflammation in the normal gland, which maintained its standard tissue morphology, with no histological signs of pancreatitis. Moreover, ECT did not induce pathological alteration of the main pancreatic duct, main bile duct, duodenum, and peri-pancreatic vessels. The results of this study demonstrated that ECT of experimental pancreatic cancer is safe, with no side effects on the normal pancreas surrounding the tumor. In few experimental cases, intraoperative ECT was performed on the small bowel [#1] and the proximal duodenum [#2]. Intraoperatively, a moderate vasocostriction of the splanchnic blood vessels was observed, with no further consequences either during or after surgery. The autopsy of terminated animals showed no macroscopic perforation of the bowel and the pathological examination revealed preserved organization of the intestinal villi and cell necrosis.

At present, there is a clinical phase I/II study, conducted at the National Cancer Institute, "*G. Pascale Foundation*" of Naples, Italy, that has the aim to evaluate both feasibility and safety of ECT in the multimodal treatment of pancreatic cancer in patients with locally advanced disease and unfit for radical surgery. Eleven consecutive patients [6 female and 5 male] from November 2011 to June 2014 were enrolled in this prospective study, 4 patients with head pancreas tumor and 7 patients with body/neck tumor pancreas. Inclusion criteria were: age between 18 and 80 years; good mental health; life expectancy $\geq$3 months; histologically confirmed diagnosis of pancreatic adenocarcinoma or pancreatic neuroendocrine tumor; locally advanced disease [stage III]; unfit for curative surgery. Patients should not have the following exclusion criteria: pregnancy positive test for women, significant heart disease, coagulation disturbances, allergy to bleomycin, lung and kidney dysfunction, implanted defibrillator or pacemaker, concomitant presence of distant metastases. All patients enrolled in this clinical trial with diagnosis of pancreas locally advanced adenocarcinoma received systemic chemotherapy before ECT treatment.

Two chemotherapy regimens were adopted: Gemcitabine + Oxaliplatin [GEMOX] in seven [7/11, 63.6%] patients and 5-FU/Leucovorin, Irinotecan, and Oxaliplatin [FOLFIRINOX] in four patients [4/11, 36.4%]. Chemotherapy was administrated 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. ECT is carried on intraoperatively, using IV bleomycin [150 UI/m^2] before the application of electrical pulses to the target area.

Preoperative imaging included CT and MR examinations: mean time between preoperative radiological evaluation and ECT was nine days [range 7–14]. Mean time between ECT and first radiological evaluation was 36 days [range 31–43].

After ECT, eleven patients were subjected to CT and only 5 patients were subjected to morphological and functional MR [about one month after ECT].

For each of 5 patients no significant reduction of maximal tumor diameter was observed in CT and MR imaging procedures [percentage change of the maximal tumor diameter calculated before and after treatment]. According to RECIST criteria, all lesions were not responder [percentage difference of maximum diameter is inferior to 30%]. Instead, using functional MR parameters significant reduction of viable tumor tissue in electrochemotherapy