RESEARCH ARTICLE

Potential Role of Electrochemotherapy as Anticancer Treatment for Cutaneous and Subcutaneous Lesions

Anna Zygogianni[1,2]*, George Kyrgias[2], John Scarlatos[3], Michael Koukourakis[4], Kyriakos Souliotis[5], John Kouvaris[1], Nikolaos Kelekis[6], Vassilis Kouloulias[6]

Abstract

Background: The aim of this study was to investigate whether electrochemotherapy is a clinically and cost-effective treatment option against skin tumors. Materials and Methods: We performed an analysis of the current literature based on database searches in PubMed/MEDLINE and we included articles till July 2012. Terms used for the search were 'electrochemotherapy', 'skin cancer', 'recurrence', and 'cutaneous and subcutaneous tumors'. Only papers published in English were included. In addition, we performed an analysis of the cost effectiveness of the method. Results: The combination of physics and chemistry is the foundation for electrochemotherapy and its efficacy, independent of the tumor histology. Clinical data showed that ECT is well tolerated and can be used in difficult cases without other available treatment options. The analysis also showed that the treatment is feasible and cost-effective. Conclusions: Electrochemotherapy is a clinically efficient safe and cost-effective treatment and clinicians should not hesitate to use it as alternative therapeutic modality or as palliative treatment.

Keywords: Electrochemotherapy - efficacy - cost-effectiveness analysis - skin lesions

Asian Pac J Cancer Prev, **17 (8)**, 3753-3757

Introduction

Cancer treatment has evolved over the last two decades, with multi-modality therapy being the mainstay of care, in an effort to achieve local tumor control. Multi-modal treatment may consist of some combination of surgery with radiotherapy or chemotherapy with hyperthermia, depending on the stage and type of neoplasm. Nevertheless, these approaches are often associated with serious side effects for the patient and high costs for the health care system.

Electrochemotherapy (ECT) is a novel technique that has been recently added in clinical practice as a complementary treatment for superficial metastases. The combination of physics and chemistry is the foundation for ECT. The application of electric pulses to the tumor tissue induces the formation of pores across the plasma membrane. The pores allow poorly permeant drugs to enter cells (Mir et al., 2001) enhancing in this way their efficacy.

ECT has a short application time and due to its favorable safety profile can be used on an out-patient basis. This, together with the relatively low cost of the technology suggests that ECT could potentially be a cost-effective treatment option for all health care systems. Still, the role of ECT in the treatment of different tumor types has not yet been well defined.

The aim of this manuscript was to investigate the clinical and cost effectiveness of ECT in the treatment of cutaneous and subcutaneous tumors.

Materials and Methods

We performed a review of the current literature based on database searches in PubMed/MEDLINE and included articles published until July 2012. Terms used for the search were 'electrochemotherapy', 'skin cancer', 'recurrence', and 'cutaneous and subcutaneous tumors'. Publications included in the reference list of articles identified through the database search and considered suitable were manually searched for. Only papers published in English were included.

Results

Definition of ECT

ECT is a new treatment modality for tumor ablation, suitable for the local control of various types of solid tumors. ECT is an alternative solution for tumor ablation

[1]1st Department of Radiology, Radiotherapy Unit, Aretaieion University Hospital, [6]2nd Department of Radiology, Radiotherapy Unit, ATTIKON University Hospital, Medical School, Kapodistrian University of Athens, [3]Radiotherapy Department, Agios Savvas Anticancer Hospital, Athens, [2]Radiotherapy Department, Larisa University Hospital, Medical School, Thessaly, [4]Radiation Oncology Clinic, Alexandroupolis University Hospital, Medical School, Thrace, [5]Faculty of Social Sciences, University of Peloponnese, Greece
**For correspondence: annazygo1@yahoo.gr*

using electroporation. Exposure of cells to electric pulses increases the citotoxicity of suitable drugs augmenting the membrane permeability. ECT thus enables chemotherapeutic agents to enter cells increasing their effectiveness (Sersa et al., 1995; Mir et al., 1998) .The most convenient drug is bleomycin (Mir et al., 1991)

Cell electropermeabilization facilitates the free diffusion of bleomycin inside the cells. This drug causes single stranded and double stranded DNA breaks, thus leading the cell in death during the mitotic phase of his division. Bleomycin can be delivered intravenously or intratumorally (Skarlatos et al., 2011). In intravenous administration, the drug enters in the cells provoking mitotic death while in intratumoral delivery, the death emanates from the necrosis that is caused in the cells with their exposure to the electric field.

Apart from bleomycin, cisplatin is also used (Sersa et al., 2000). Cisplatin is a low permeant drug that is active on many tumors. Good antitumor effectiveness can be obtained by either of the drugs (Jaroszeski et al., 2000).

Principles of ECT

ECT is indicated in the local treatment of cutaneous and subcutaneous metastatic lesions regardless of tumor histology and ongoing or previous treatments (Giardino et al., 2006). ECT combines delivery of chemotherapeutic drugs with application of electric pulses to the tumors to facilitate the drug administration into the cells (figure 1). Homogeneous tumor tissue electroporation is obtained using dedicated electrodes designed for cutaneous lesions, mucosa and subcutaneous tumor tissue up to a depth of 3 cm. Large tumor nodules can be treated with repeated applications of electric pulses (Miklavcic et al., 2010).

In addition, the delivery of electric pulses to tissues results in blood flow differences Specifically, in hypoperfusion of the area between and distally from the electrodes due to reflexory vasoconstriction of afferent arterioles, known as the vascular effect (Skarlatos et al., 2011).

Several other chemotherapeutic drugs have been tested in combination with the permeability of the cells, but are under investigation (Cemazar et al., 2010).

Clinical effectiveness and safety

The first clinical trial on ECT was performed by Mir et al in 1991. ECT was applied on cutaneous metastases of head and neck carcinoma patients. It showed good anticancer effectiveness. Several clinical trials followed that initial study (Mir et al., 1991).

Mir et al tried to define the standard operating procedures in order to treat cutaneous and subcutaneous nodules using ECT. In addition the application of ECT was also extended to other types of tumors (Mir eta al., 2006).

Larkin et al used the ECT in patients with cutaneous or subcutaneous tumors previously refractory to surgical intervention, systemic chemotherapy, and/or radiotherapy and they responded successfully irrespective of histologic type. 30 patients with 111 tumors were studied. None of the treated tumors progressed. Sixty percent of tumors (66 of 111) showed complete response while 22% partial response and 18% no change. It was proved that ECT was more effective in smaller tumors (<3 cm) (Larkin et al., 2007).

Quaglino et al evaluated the clinical activity and tolerability of ECT with i.v. bleomycin, and they analyzed the response increase associated to repeated sessions in cutaneous melanoma metastases (Quaglino et al., 2008). Fourteen patients were studied and from the first application of ECT a response was obtained in 13/14 patients, with a complete regression (CR) in 7 (50%). The remaining patients were submitted in second and third application. Overall, a response was obtained in 93% of metastases and the local tumor control rate was 74.5% at 2 years (Quaglino et al., 2008).

Campana et al studied 52 patients with different cancer histotypes, mainly melanoma and breast cancer (Campana et al., 2009). The study applied ECT with bleomycin, evaluating toxicity, local response, response duration and the impact on quality of life. A total of 608 tumor nodules were treated with 27% of patients affected by nodules >3 cm in size. There was no toxicity and the objective response was obtained in 96% of the patients. Twenty two patients underwent a second treatment due to partial response or the appearance of new lesions. After a mean follow up of 9 months only two patients presented relapse in the treatment field. Quality of life was, without doubt, perceptibly improved (Campana et al., 2009).

Gargiulo et al. (2010) evaluated the ECT in patients with non-melanoma head and neck cancers Bleomycin was applied in 25 patients and a 100% objective response was observed at six weeks following initial treatment (Gargiulo et al., 2010). The complete response was 72% and the partial response was 28% according to the WHO criteria. None of the lesions with complete response relapsed in a median follow up of 18 months (Gargiulo et al., 2010).

Curatolo et al studied 23 patients with Kaposi sarcoma. After the first application of ECT patient objective response was observed in all of them (Curatolo et al., 2012). Complete response was obtained in 60.9% of patients (14/23). A second one was performed in 5 patients (21.7%) and a third one in 2 patients. Overall, complete response was observed in 65% of patients. After a median follow up of 1.5 years, 16 patients maintained the response, 4 after repeated courses. Local control of treated lesions was showed in 20 patients. The overall survival rate was 74.4% at 2 years. Toxicity was not observed (Curatolo et al., 2012).

Skarlatos et al applied ECT in cutaneous and subcutaneous nodules in 52 patients using bleomycin according to standard protocols. A complete response was observed in 63.83%, partial response in 31.91% and local control in 95.74% of patients. No toxicity was observed (Skarlatos et al., 2011). A typical treatment with ECT is shown in Figures 2-5.

Mevio et al applied ECT with bleomycin in 15 patients with head and neck cancer (Mevio et al., 2012). Electrical pulses were delivered to 31 lesions. Of these, 19 (61.5%) showed a complete response, 10 (32.5%) a partial response, 1 (3%) stable disease and one (3%) progression of the disease. The objective response two months after the procedure was 94%. All the lesions that

showed complete regression were less than 3 cm in size. After a follow-up of 2 to 20 months, 29% of the patients were alive and disease-free, 50% were alive with disease, 14% died due to the disease and 7% died due to other causes (Mevio et al., 2012).

Campana et al applied ECT in 35 patients with cutaneous chest wall recurrence from breast cancer after mastectomy who presented with progression despite re-irradiation and extensive systemic treatments (Campana et al., 2012) In 516 skin nodules, response was assessed on 196 lesions (median size 20 mm, range 10-220). Two-month objective response rates were: 54.3 % complete (19/35 patients), 37.1 % partial (13/35), and 8.6 % with no change (3/35). Median follow-up was 32 months and the three-year local control rate was 81 %. Related morbidity was mild, increased after retreatments and consisted primarily of pain and dermatological toxicity (Campana et al., 2012).

Matthiessen et al studied ECT in two studies (Matthiessen et al., 2011; Matthiessen et al., 2012). The first study evaluated 52 patients with cutaneous metastases. Complete and partial response rates were 68% and 18%, respectively, for cutaneous metastases <3 cm and 8% and 23%, respectively, for cutaneous metastases >3 cm. Toxicity was not observed, including the elderly (Matthiessen et al., 2011).

The second study by Matthiessen et al evaluated 15 heavily pre-treated patients with cutaneous recurrences from breast cancer where no further treatment options were available. Specifically, the clinical response and the toxicity by PET/CT were assessed. The patient objective response was 86%. In a median follow up bigger than 8 months CT showed four (33%) patients achieving over 50% tumor volume reduction, clinical examination showed one complete response and one partial response. Symptomatic relief included decreasing exudates, odor, and bleeding. Treatment was well tolerated; the main side effect was post-treatment pain (Matthiessen et al., 2012). Clinical trials with ECT are shown in Table 1.

Cost effectiveness

Colombo et al. (2008) performed a cost-effectiveness analysis, comparing the costs and clinical benefits of ECT (Cliniporator™) versus other currently used methods such as isolated limb perfusion, radiotherapy,chemotherapy, interferon-alpha (TNFα), and hyperthermia for the treatment of cutaneous or subcutaneous advanced tumors (Colombo et al., 2008). The analysis accounted for the direct health costs associated with each treatment pathway, from the perspective of the Italian National Healthcare System.

The analysis showed that ECT was cost-effective with an incremental cost effectiveness ratio (ICER) of €1,572. Although isolated limb perfusion was the most effective among all treatment strategies, it was also the most expensive due to the use of TNFα. Combination treatment with hyperthermia, radiotherapy, chemotherapy

Table 1. Clinical studies with ECT

Studies	No pts	CR	PR
Larkin et al (2007)	30	16	22
Quaglino et al (2008)	14	50	50
Campana et al (2009)	52	80	20
Gargiulo et al (2010)	25	72	28
Curatolo et al (2012)	23	65	35
Skarlatos et al (2011)	52	63.8	31.9
Mevio et al (2012)	15	61.5	32.5
Campana et al (2012)	35	54.3	37.1
Matthiessen et al (2011)	52	68	18
Matthiessen et al (2012)	15	6.6	6.6

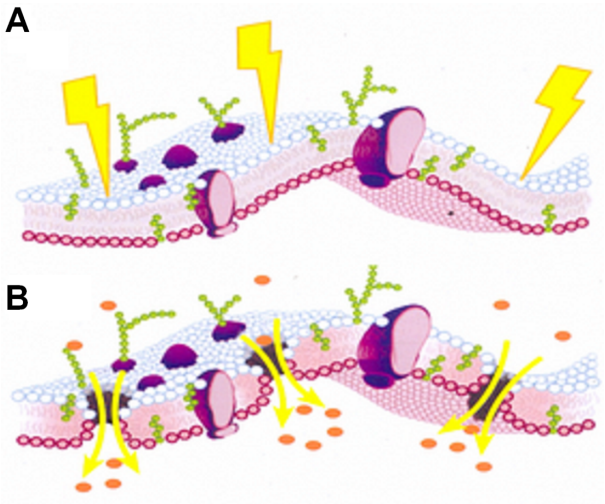

Figure 1. Intraceccular Mechanism of ECT.

Figure 2. Patient Presenting with Cutaneous Metastatic Lesion at the Skin

Figure 3. ECT with the Electrodes during Application.

Figure 4. Irradiation with Electron Beam at the Lesion

Figure 5. Treatment Outcome Showing a Complete Response

and TNFα was more costly and less effective, and was thus dominated by ECT. Radiotherapy and TNFα used as monotherapies were the least effective. The authors concluded that the favorable cost effectiveness ratio of ECT justify its wider use (Colombo et al., 2008).

Recently ECT was approved by the Central Health Committee of the Greek Ministry of Health as a clinical method for anticancer treatment. It is already included in the total cost of €2000 with two-days hospitalization.

Discussion

In Europe 100 centers are already equipped with ECT equipment offering the new technology to their patients. The potential clinical applications of ECT render it an approach of scientific interest. Clinical data showed that ECT is well tolerated and can be used in difficult cases without available treatment options (Mir et al., 1991; Mir eta al., 2006; Larkin et al., 2007; Quaglino et al., 2008; Campana et al., 2009; Gargiulo et al., 2010; Skarlatos et al., 2011; Matthiessen et al., 2011; Curatolo et al., 2012; Mevio et al., 2012; Campana et al., 2012; Matthiessen et al., 2012; Solari et al., 2014; Di Montana et al., 2014).

According to the studies presented above, the complete response rate for lesions > 3 cm in maximum diameter was lower than that obtained in smaller lesions. Specifically, Curatolo et al concretely found that the lesions bigger than 3 cm compared with smaller ones had complete response 47.1% versus 61.1% respectively (x^2 test, P=0.007) (Curatolo et al., 2012).

Moreover, Quaglino et al showed that repeated ECT sessions are associated with a response increase in re-treated lesions which could allow to overcome the reduced activity in >1 cm sized metastases (Quaglino et al., 2008).

Head and neck cancers are most often associated with a high risk of relapse. This disease is usually controlled with local treatments. ECT is indicated for these lesions. Gargiulo et al showed that nodule objective response was 100% and that ECT is effective as first line and as neoadjuvant treatment (Gargiulo et al., 2010).

In addition, it was shown that in melanoma and other skin tumors (Quaglino et al., 2008; Campana et al., 2009; Curatolo et al., 2012) the patient objective response was 93% in the study by Quaglino et al. (2008) , 96% by Campana et al and 100% by Curatolo et al. The palliation of bleeding and painful lesions occurs within a few days of the treatment. Complete response is confirmed by the absence of tumor cells, as shown by histological analysis (Quaglino et al., 2008). Moreover, a meta-analysis by Clarke et al demonstrated that the association of systemic and local control in breast cancer treatment improves by 4.9% the overall survival at 15 years (Clarke et al., 2005) 22. Clinical evidence from multiple independent reports (Larkin et al., 2007; Campana et al., 2009; Matthiessen et al., 2012). demonstrated that ECT is an effective treatment for local recurrence and skin metastases from breast cancer, with an objective response of 85% (85%, 96% and 86% respectively).

No serious adverse events were observed based on the available data. Reported adverse events were flu-like symptoms occurring one to two days after treatment, pain in the treated area one to two days after treatment, ulceration of treated area, cough, allergic skin reaction and anxiety (Matthiessen et al., 2011). There was no skin toxicity grade 3 or 4 (Mir et al., 1991; Mir eta al., 2006; Larkin et al., 2007; Quaglino et al., 2008; Campana et al., 2009; Gargiulo et al., 2010; Skarlatos et al., 2011; Curatolo et al., 2012; Mevio et al., 2012; Campana et al., 2012). Most side-effects were seen and treated with oral antibiotics, administration of painkillers and creams, leading to a complete remission within a few days.

The limited complications associated with ECT combined with the simplicity in its use offer an improved quality of life for patients. ECT is performed either on an out-patient basis, or during a one-day hospitalization, while the median treatment time is 25 minutes, saving time and cost for the patient and the health care system. In the case of out-patient treatment patients are released from the hospital within an hour in the case of local anaesthesia or after approximately 3 hours in the case of general anaesthesia (Marty et al., 2006). After treatment, a satisfactory cosmetic effect is obtained, without need for a specific dressing of the treated area, while the first regular check up is planned one or two months later, allowing patients to return immediately to everyday life activities.

Moreover, the cost of the technology is relatively low and its use does not require any specific skill or long training of the physicians. Thus, ECT could be considered as a treatment alternative by all health care systems, and specifically by small hospitals, or developing countries with tight budget constraints (Marty et al., 2006). Colombo

et alconfirmed the cost-effectiveness of ECT compared to other currently used cancer treatment options, however further studies should be conducted to validate these findings (Colombo et al., 2008).

Our analysis confirms the effectiveness of electrochemotherapy in the treatment or local control of recurrent or extended primary head and neck, breast, skin cancers in patients not suitable for standard therapeutic options. Based on the available evidence ECT is an efficient and safe treatment that improves patients' quality of life and contains costs. Clinicians should not hesitate to use it even in the elderly where surgery is contraindicated.

References

Campana LG, Mocellin S, Basso M, et al (2009). Bleomycin-based electrochemotherapy: Clinical outcome from a single institution's experience with 52 patients. Ann Surg Oncol, 16, 191-9.

Campana LG, Valpione S, Falci C, et al (2012). The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. *Breast Cancer Res Treat*, **134**, 1169-78.

Cemazar M, Jarm T, Sersa G (2010). Cancer electrogene therapy with interleukin-12. *Curr Gene Ther*, **10**, 300-11.

Clarke M, Collins R, Darby S, et al (2005). Effects of radiotherapy and the differences in the extent of surgery for early breast cancer on local reccurence and 15 year survival: an overview of the randomized trials. *Lancet*, **366**, 2087-106.

Colombo GL, Matteo SD, Mir LM (2008).Cost-effectiveness analysis of electrochemotherapy with the Cliniporator trade mark vs other methods for the control and treatment of cutaneous and subcutaneous tumors. *Ther Clin Risk Manag*, **4**, 541-548.

Curatolo P, Quaglino P, Marenco F, et al (2012). Electrochemotherapy in the treatment of Kaposi sarcoma cutaneous lesion: a two center prospective phase II trial. *Ann Surg Oncol*, **19**, 192-8.

Di Monta G, Caraco C, Benedetto L, et al (2014). Electrochemotherapy as "new standard of care" treatment for cutaneous Kaposi's sarcoma. *Eur J Surg Oncol*, **40**, 61-6.

Gargiulo M, Moio M, Monda G, et al (2010). Electrochemotherapy: actual considerations and clinical experience in head and neck cancers. *Ann Surg*, **251**, 773.

Giardino R, Fini M, Bonazzi V, et al (2006). Electrochemotherapy: a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues. *Biomed Pharmacother*, **60**, 458-62.

Jaroszeski MJ, Dang V, Pottinger C, et al (2000). . Toxicity of anticancer agents mediated by electroporation *in vitro*. *Anticancer Drugs*, **11**, 201-8.

Larkin JO, Collins CG, Aarons S, et al (2007). Electrochemotherapy: Aspects of preclinical development and early clinical experience. *Ann Surg*, **245**, 469-79.

Marty M, Sersa G, Garbay JR, et al (2006). Electrochemotherapy - an easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: results of the ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. *Eur J Cancer*, **4**, 3-13.

Matthiessen l, Chalmers R, Sainsbury DC, et al (2011). Management of cutaneous metastases using electrochemotherapy. *Acta Oncol*, **50**, 621-9

Matthiessen L, Johannesen H, Hendel H, et al (2012). Electrochemotherapy for large cutaneous recurrence of breast cancer: A phase II clinical trial. *Acta Oncol*, **51**, 713-21.

Mevio N, Bertino G, Occhini A, et al (2012). Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. *Tumori*, **98**, 308-13.

Miklavcic D, Snoj M, Zupanic A, et al (2010). Towards treatment planning and treatment of deep seated solid tumors by electrochemotherapy. *Biomed Eng Online*, **9**, 10.

Mir LM, Orlowski S, Belehradek Jr, et al (1991). Electrochemotherapy potentiation of antitumour effect of bleomycin by local electric pulses. *Eur J Cancer*, **27**, 68 -72.

Mir LM, Glass LF, Sersa G, et al (1998) Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. *Br J Cancer*, **77**, 2336-42.

Mir LM (2001) Therapeutic perspectives of in vivo cell electropermeabilization. *Biochemistry*, **53**, 1-10.

Mir LM, Gehl J, Sersa G, et al (2006). Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the CliniporatorTM by means of invasive or non-invasive electrodes. *EJC (Suppl)*, **4**, 14-25.

Quaglino P, Mortera C, Osella-Abate S, et al (2008). Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. *Ann Surg Oncol*, **15**, 2215-22.

Sersa G, Cemazar M, Miklavcic D (1995). Antitumor effectiveness of electrochemotherapy with cis-diamminedichloroplatinum(II) in mice. *Cancer Res*, **55**, 3450-5.

Sersa G, Stabuc B, Cemazar M,et al (2000). Electrochemotherapy with cisplatine: clinical experience in malignant melanoma patients. *Clin Cancer Res*, **6**, 863-7.

Skarlatos I, Kyrgias G, Mosa E, et al (2011). Electrochemotherapy in cancer patients: first clinical trial in Greece. *In vivo*, **25**, 265-74.

Solari N, Spagnolo F, Ponte E, et al (2014). Electrochemotherapy for the management of cutaneous and subcutaneous metastasis: a series of 39 patients treated with palliative intent. *J Surg Oncol*, **109**, 270-4.