

Use of electrochemotherapy in a case of neck skin metastasis of oral squamous cell carcinoma: Case report and considerations

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ABSTRACT: *Background.* Squamous cell carcinoma (SCC) is the most common oral cavity malignant tumor. Surgery, radiotherapy, and chemotherapy have been the major options for its treatment. Electrochemotherapy (ECT) is a novel local treatment successfully used in secondary or primary skin or subcutaneous tumors. This new cancer treatment is a modality in which a locally applied electrical field enhances cell membrane permeability, thereby allowing greater intracellular accumulation of a chemotherapeutic agent.

Methods. We report a case of a man affected by an ulcerated SCC. The man was treated with ECT with good results.

Results. In our case, ECT was successful in the management of extensive metastasis of SCC in clinical conditions, whereas other approaches were rejected.

Conclusion. This case shows good clinical results; however, other studies are necessary to show that ECT should be considered as a promising treatment option. © 2014 The Authors. Head & Neck Published by Wiley Periodicals, Inc. *Head Neck* 36: E86–E90, 2014

KEY WORDS: electrochemotherapy, oral cancer, skin metastasis, neck, bleomycin

INTRODUCTION

Cancer remains a leading cause of mortality despite advances in understanding, detection, and treatment of this disease. Electroporation-based cancer treatment approaches are currently undergoing intensive investigation in the field of drug delivery. Their first biomedical application in the treatment of cancer came in the form of electrochemotherapy (ECT), which, since its beginnings in the late 1980s, has evolved into a clinically verified treatment approach for cutaneous and subcutaneous tumor nodules.¹

The use of high-voltage electrical pulses causes the formation of pores in cell membranes with reversible damage that increases the uptake of molecules including drugs into the cells.²

The cell membranes are reversibly electroporated at given electrical parameters, including the field strength and duration of the pulses. Electroporation has been used to enhance the delivery and diffusion of chemotherapeutic drugs, such as cisplatin and bleomycin, in cancer cells and solid tumors, respectively.^{3,4} Since the first clinical study in 1990, ECT has been reported as highly effective, with complete response rates between 60% and 70% and

objective response (complete and partial response) rates of approximately 80%,^{1–5} especially when the standard operating procedures for ECT were followed. ECT is routinely used in the treatment of cutaneous and subcutaneous tumors, metastases of melanoma, Kaposi sarcoma, Merkel cell carcinoma, basal cell carcinoma, and chronic lymphocytic leukemia infiltration⁶ because of its high effectiveness, safety, limited toxicity, simplicity, cost-effectiveness, organ-sparing effect, and its suitability for repetitive and neoadjuvant treatment.⁷

The effectiveness of treatment depends on the extracellular drug concentration at the time of the electroporation pulse delivery, the distribution of the electric field inside the tumor, the patient characteristics (age, sex, and health status), and the tumor and treatment characteristics (tumor type, size and location, drug type, electrode type, dose and route of administration, and protocol of electroporation pulse delivery) that most likely contribute to the variability observed in the tumor response to ECT.

With approval of the Patient and Review Board on Biomedical Research of the Department of Surgical Biotechnologies and Science of the “Sapienza” University of Rome, we report a case of a man affected by ulcerated squamous cell carcinoma (SCC) of the neck skin. In this case, other treatment approaches had been rejected, and the patient was treated with ECT with good results.

CASE REPORT

A 63-year-old white man was referred to us with a solitary nodule on the right side of the neck that had

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FIGURE 1. Before treatment, single erythematous painless, erythematous, dome-shaped nodule with suppurative foci was present on right side of the neck near the surgery sutures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

appeared 2 months after the surgical removal of a SCC of the floor of the oral cavity.

This carcinoma was focused on the middle of the tongue on the right side with a limited extension to the adjacent oral floor. The neoplasm was >4 cm, and there was involvement of the right neck nodes at levels I, II, and III with skin adhesion and ulceration. One of these nodes had a diameter of >6 cm. According to the 2010 American Joint Committee on Cancer TNM Classification of Tumors of the oral cavity, it was cT3N3M0 (stage IVB).

In accordance with the National Comprehensive Cancer Network guidelines (2011), the surgical treatment was an excision of the primary tumor of the tongue and oral floor (a pull-through operation) and ipsilateral neck dissection (levels I, II, III, IV, and V) with ablation of the skin involved with the tumor. A secondary reconstruction with a myocutaneous pectoralis major muscle flap with 2 skin isles was used for reconstruction of the oral mucosa and laterocervical skin.

The histopathology was characterized by a poorly differentiated SCC (G3) of the oral cavity. The dissection of the neck nodes showed metastases with extracapsular spread and skin infiltration. The final histopathological classification was pT3N3M0 (stage IV).

The patient reported that the skin nodule was growing rapidly. He had a painless, erythematous, dome-shaped nodule with suppurative foci on the right side of the neck near the surgical suture. The nodule ranged from 4 × 4 cm in diameter (Figure 1). An incisional biopsy specimen revealed small and round cells with infiltration of the underlying connective tissue. On the basis of the histopathological features, SCC was diagnosed.

The 2011 National Comprehensive Cancer Network guidelines advise surgery or chemoradiotherapy, and this case was discussed with the Oncological Tumor Board of the Department of Organs of Sense of the “Sapienza” University of Rome. The patient refused other major surgical treatments, as well as chemotherapy or radiotherapy. In this condition, we decided to treat the patient with



FIGURE 2. The lesion 1 week after treatment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ECT because a review of the international literature showed that it had good results and was indicated for all relapsing tumors of the skin regardless of the dimensions and histological types. If the treatment with ECT had failed, surgery or chemoradiotherapy treatments were possible as additional treatment options.

The patient was treated with ECT with intravenous sedation and local anesthesia. Eight minutes after 15 mg/m² of intravenous bleomycin therapy was begun, a needle electrode-hexagonal array (length, 25 mm) was inserted directly into the tumor mass. A series of 8 pulses of 1000 V/cm was delivered at a frequency of 5 kHz and duration of 100 microseconds. To ensure that the lesional tissue received an adequate concentration of bleomycin, the treatment was completed 30 minutes after the end of the infusion. A sterile medication was applied on the treatment site.

The patient had no residual pain, fever, or discomfort after the treatment and was discharged the next day. When the sterile dressing was removed after 7 days, the tumor mass was detached (Figure 2). Two months after treatment, the lesion was diminished in diameter and the



FIGURE 3. The lesion 3 months after treatment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

absence of disease recurrence was confirmed by an incisional biopsy.

Three months after the treatment, the lesion had disappeared and the skin was completely sheltered (Figure 3). Two years after the treatment, the patient currently shows no signs of local or systemic disease recurrence.

DISCUSSION

ECT is a tumor ablation modality that is safe and effective on any type of solid tumor of the skin. Its use is standardized to skin and subcutaneous localizations, regardless of the histological origin of the tumor. ECT is a local antitumor therapy; however, new approaches are currently being developed for the treatment of deep-seated tumors.^{8,9}

The key issue in ECT is to ensure that the drug is present in the tumor when the electric pulses are applied. Bleomycin can be delivered intratumorally or systemically, whereas cisplatin should be injected intratumorally to achieve the best results. When the drug is delivered systemically, the electric pulses should be delivered to the tumor site during the pharmacokinetic peak, which was reported to be between 8 and 28 minutes in humans¹⁰; for the intratumoral applications, the pulses should be delivered from 1 minute to 10 minutes after the drug injection.¹¹

ECT is typically used as a local antitumor therapy of skin or subcutaneous tumors that combines a non-permeant or poorly permeant cytotoxic chemotherapeutic agent (eg, bleomycin or cisplatin) and short, high-voltage electrical pulses to increase the drug delivery into the cells. Electroporation transiently permeabilizes the tumor cell membranes, enabling diffusion of a chemotherapeutic drug, such as bleomycin or cisplatin into the cells and increasing the cytotoxicity of the drug.^{9,12–16}

These drugs are hydrophilic and lack transport systems in the membrane so that they do not pass the cell membrane in normal conditions. The electroporation of the cells potentiates the cytotoxicity of bleomycin up to several thousand-fold, as reported by Mir¹⁷ and confirmed by several consecutive studies.¹⁸ The cytotoxicity of bleomycin is primarily because of direct DNA damage. The cells are killed because some of the DNA breaks remain unrepaired, and the cytotoxicity is revealed when the cells try to divide because their chromosomes are fragmented, whereas the quiescent nondividing cells remain alive. This mitotic cell death process results in a selective killing of the dividing (tumor) cells that actually spares the nondividing (normal) cells around the treated tumor. The normal tissues located in proximity to the tumor nodule are often infiltrated by tumor cells that can originate disease relapse after an unpredictable period of time. Because of the aggressiveness of the classic tumor treatments, the margins are not extensively treated. In the case of the intravenous delivery of bleomycin, the amounts of bleomycin in the interstitial fluids of the tumor and thus the amount of bleomycin entering the cells provoke the mitotic cell death process described above. This situation opens the possibility of safe treatment of large margins around the treated nodules.¹⁷

In addition, ECT provokes a transitory local ischemia and permanent vascular damage, reducing the tumor vascularization. In addition to the membrane electroporation,

the application of electric pulses to tissues induces a transient but reversible reduction of blood flow.¹⁹ The 80% decrease in the tumor blood flow immediately after the application of the electric pulses induces drug entrapment in the tissue for several hours, providing more time for the drug to act.¹⁹

The vascular effect implies that at the time when the cell is permeabilized, the drug is held within the electroporated area by the so-called “vascular lock.” It has been shown that in tumors, the vascular lock lasts much longer than in normal tissues. The restoration of the initial blood flow levels may require hours. These modifications in the blood flow could be particularly advantageous for intratumoral drug injection, as this effect would decrease the drug washout. The blood flow returns to normal in tumors within 24 hours after the application of the electric pulses, whereas in the normal tissues, the restoration is faster, within several hours.²⁰ The cytotoxic effect of ECT is not limited to the cells in the tumors. ECT also acts on the endothelial cells in the lining of tumor blood vessels, resulting in their death, abrogation of the tumor blood flow, and a consequent cascade of tumor cell death surrounding the vessels. This vascular disrupting mechanism of ECT contributes to its antitumor effectiveness and has been demonstrated for bleomycin and cisplatin.²¹

It seems that ECT is responsible for an autoimmune response that is selective for neoplastic cells. Shortly after the initial preclinical trials on ECT, it was shown that the host immune response participated in the successful cures after treatment with ECT.²²

Because of massive tumor antigen shedding in organisms after ECT, systemic immunity is induced and can be upregulated by additional treatment with biological response modifiers, such as interleukin-2, interleukin-12, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor- α .²³

Whether ECT is administered with the patient under general anesthesia or local anesthetics depends on the patient, the physician, and the number and size of the tumors.

We describe a clinical case and course of a patient with a skin relapse of SCC of the neck who showed clinical regression after ECT.

The standardization of ECT was developed through a multicentric study (European Standard Operating Procedures of Electrochemotherapy [ESOPE]). The objective response was 85%, a complete response was 73.7%, and a prospective nonrandomized multi-institutional study was needed. This study was conducted by a consortium of 4 cancer centers in the ESOPE project funded under the European Commission’s 5th Framework Program. The treatment response after ECT was tested according to the tumor type, the drug used, the route of its administration, and the type of electrodes used.¹⁴ The results of this study are summarized as follows: an objective response rate of 85% (a 73.7% complete response rate) was achieved for ECT-treated tumor nodules, regardless of the tumor histology and drug or route of administration used. The local tumor control rate for ECT was 88% with bleomycin given intravenously, 73% with bleomycin given intratumorally and 75% with cisplatin given intratumorally, demonstrating that the approaches were equally effective in local tumor control. In all the clinical studies reported

to date, including the ESOPE study, 288 patients have been treated as follows: 782 tumor nodules were treated by ECT with bleomycin, and 398 tumor nodules were treated by ECT with cisplatin. The results of the ESOPE study are comparable to the previously reported results on the effectiveness of ECT.¹⁴

The standard operative procedures provide for the use of a generator of electric pulses. The prerequisite for effective ECT is a sufficient drug concentration and distribution within the tumor, as well as an adequate electric field distribution. The exact procedures for the systemic or local drug delivery using bleomycin or cisplatin, followed by the application of electric pulses, should be followed for each specific clinical condition. The standard operating procedure guidelines for using a Cliniporator electric pulse generator (IGEA, s.r.l. Carpi, Modena, Italy) has recently been published. The European Commission first funded the Cliniporator (QLK3-1999-00484) project that led to the development of a novel device, the Cliniporator, which is now available to all oncologists and can be used in clinical practice.

The dose for bleomycin by intravenous injection is 15,000 IU/m², for intratumoral injection, the dose for bleomycin is approximately 500 IU/cm, and for cisplatin, approximately 1 mg/cm, depending on the tumor volume.⁹ The electric pulses are in most reported cases delivered at 8 pulses of 100 ms duration at 1 Hz, or more recently, at a 5 kHz repetition frequency. These pulses were shown to be optimal for the cell penetration of "small drugs," such as bleomycin and cisplatin, provided that the local electric field established in the target tissue (ie, the tumor) was sufficiently high.¹⁴ In the clinical trials, the field strengths that have been used are between 800 and 1300 V/cm (the ratio of the applied voltage to the electrode distance), depending on the electrodes used.¹⁰

Although in principle there are different types of electrodes available on the market, the following 2 types of electrodes exist: plate electrodes and needle electrodes. Plate electrodes are used for the treatment of skin or superficial lesions. Needle electrodes are of the following 2 types: needles positioned in 2 parallel rows or in a circular (hexagonal) array. In contrast to plate electrodes, needle electrodes must be inserted through the tumor tissue to the deep tumor border.³ A major disadvantage of plate electrodes is that it is difficult to be certain that the electric field reaches the deepest parts of the tumor.²⁴ Regardless of the type of electrode, the electric field is highest around the electrode and between the electrodes, but is reduced very rapidly outside the electrode array. Thus, if the tumor is larger than the distance between the electrodes, the entire tumor can be efficiently treated by moving and placing the electrodes adjacently for each consecutive electric pulse application.

The indications for ECT are all primitive or relapsing tumors of the skin or subcutaneous tissue, with variable dimensions from 0.3 cm to 20 cm of every histological type. The sizes of the treated tumors were markedly variable, from small malignant melanomas of 0.3 cm²⁵ to cutaneous nodules from head and neck SCCs of 5 cm²⁶ and breast metastases with cutaneous infiltration measuring 8 × 20 cm¹⁰. The best results in the literature have been achieved with fibrosarcomas and basocellular carcinomas.

The most common side effect noted is an involuntary muscle contraction at the instant of the electric pulse. The contraction stops at the end of the pulse. It is generally painless; however, there is some discomfort. In cases in which the patients were treated with plate electrodes, burning of the skin was sometimes observed, which was not observed in the cases in which needle electrodes were used.²⁷

The major disadvantage of ECT is that it cannot be used for the treatment of deep tumors because only electrodes for treatment of cutaneous and subcutaneous tumors have been designed and produced. Comparative studies with other local treatments, such as radiotherapy and isolated limb perfusion should be initiated. For safety reasons, ECT is not recommended in patients with cardiac pacemakers and patients on anticoagulant therapy.¹

This case report demonstrates that ECT is an effective therapeutic solution for metastasis or local SCC recurrence. Our experience confirmed the importance of ECT as an effective therapeutic approach. It is simple, relatively inexpensive, safe, and can be repeated. Treatment with ECT provides an option for more conservative surgery and an improved cosmetic effect, with less extensive postoperative damage and complete control of localized tumors leading to a good quality of life.

CONCLUSIONS

The content of this article should allow physicians to understand the potential of ECT, and the standard operating procedure should provide the information required for the application of ECT. To facilitate the dissemination of ECT, the partners of the European (EU) projects have defined training programs to demonstrate the methodology. The physicians that received 1 day of training now treat patients at their institutions with ECT.

In most patients, ECT can be applied under an outpatient basis, and the cost benefit ratio is very favorable because bleomycin and cisplatin are inexpensive drugs and the equipment necessary for ECT is much less costly than an ionizing radiation device.

ECT with bleomycin or cisplatin is effective for localized tumor control of cutaneous and subcutaneous tumor nodules of different histologies, resulting in up to approximately 75% long-term complete response of the treated tumors. After the progression of ECT into broader clinical practice, gene electrotransfer for gene therapy will be the next development of ECT.

We hypothesize that ECT is an effective and safe therapy in primary and relapsing head and neck tumors of the skin. The treatment is repeatable and does not exclude the subsequent use of the traditional therapies. We suggest that in the tumor therapy guidelines, ECT should be considered among the options for treatment that include surgery, radiotherapy, and chemotherapy. Other studies on this promising technique are necessary to prove that ECT should be considered to be a treatment option.

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