Life Sciences Student Journal
2025, Vol3, No2 pp 14-20
DOI:10.22034/LSSJ.2025.144

Effective treatment of GIST metastasis by electrochemotherapy with high frequency and low voltage: Case report study

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Ph.D. in Medical Physics

Article Type:
Research article

Article Info:
Received: 6 April . 2025
Revised: 9 April .2025
Accepted: 16 April .2025
ePublished: 18 April .2025

Key words: Electrochemotherapy, Low voltage, High frequency, Bleomycin

Abstract

Electrochemotherapy (ECT) involves the use of electrical pulses to enhance the uptake of chemotherapy drugs such as bleomycin and cisplatin in solid and surface tumor cells, which has become a valuable treatment option in oncology. Which is not only useful as a palliative treatment but also a safe treatment approach. This method guarantees the best possible results in the minimum number of sessions and reduces complications. During this method, fewer chemotherapy drugs are used and the patient experiences muscle contractions due to high amplitude and low repetitions. Electrochemotherapy with high frequency and low voltage (LVHF) has been developed and optimized in vitro and in vivo and can be used in the clinic. In the present study, a case of Gist metastasis in the abdomen is reported. In this case, LVHF ECT was used to reduce the size and relieve the pain and symptoms of metastasis to the abdominal region in clinical conditions. Our electrochemotherapy method shows good clinical results and according to World Health Organization (WHO) standards, the tumor responded partially to the treatment. However, further studies on this new method are necessary to prove that LVHF ECT can be considered a standard treatment method.

Keyword: again, gut microbiome, cognitive decline, aerobic training, sarcopenia

1. Introduction

Electrochemotherapy is the use of special chemotherapy drugs with electrical pulses that are applied to tumor nodules. Local use of electrical pulses on the tumor increases drug delivery to the cells (1). Electroporation is a physical approach to enhance the delivery of cytotoxic drugs to tumors. In electroporation, electrical pulses are applied to the tumor, creating transient pores in the tumor cell membrane, thereby increasing the permeability of the cell membrane for the entry of hydrophilic drugs into the cytoplasm and inducing cell death (2). The use of ECT in humans was initially limited to local palliative treatment for melanoma skin metastases. ECT is currently used

mainly in Europe as an adjunctive therapy to treat tumors that are resistant to conventional treatments such as radiotherapy or chemotherapy or those that cannot be surgically removed due to their distribution and location. In addition, it can be used as cell therapy in organ preservation. In this method, before removing the tumor through surgery, to reduce the size of the tumor, several sessions of electrochemical therapy are performed (3, 4). Among the many drugs that have been tested so far, bleomycin and cisplatin are the drugs of choice for ECT, as they are already recognized as treatments for several types of cancer and have shown the greatest increase in efficacy in preclinical and clinical trials (5, 6). Clinical data collected in several clinical studies show that approximately 80% of cutaneous and subcutaneous tumor nodules respond to treatment, of which approximately 70% are in complete response after a single application of electrochemotherapy (7). Usually, only one treatment is needed. However, electrochemotherapy can be repeated in several sessions, every few weeks, with the same effectiveness each time. This treatment leads to the effective eradication of treated nodules without tissue scarring (8). The electrochemical treatment protocol includes local or systemic drug injection, after which electrical pulses are applied (1). Response to treatment depends on tumor type, tumor location, tumor size, which can be from 3 mm to 5 cm in diameter, and the number of nodes (from 1 to 100) (9, 10). 0.5-1 mg/cm3 of cisplatin and 1000 -3250 IU/cm3 of bleomycin are injected into the tumor or bleomycin is injected intravenously in a dose of 15,000 IU/cm3. If the drug is injected into the tumor immediately after, and if the drug is injected intravenously, 8 to 28 minutes later, electrical pulses are used. The electric pulse generator for electrochemotherapy should deliver square wave electric pulses of amplitude 1000 V or more with repetition and frequency from 1 Hz to 5 kHz (11-13). Plate electrodes are used for small, superficial tumor nodules, needle electrodes are used to treat deeper subcutaneous nodules (1). The use of variable electrode-geometry needle electrodes overcomes two known limitations of standard ECT - large tumor size and deep anatomical location - and may be an active and safe local treatment for patients with soft tissue tumors (14). Here we report a case of GIST (Gastrointestinal stromal tumor) metastasis that developed in a large area of the abdomen where LVHF ECT was beneficial in reducing the size of the metastatic nodule and relieving the patient's symptoms.

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1-1 Case Report

A 41-year-old woman with a 9-year history of GIST was admitted to the clinical oncology department of Bu Ali Hospital in Tehran with primary surgical treatment. Her initial treatment was surgery, then 3 years of adjuvant Imatinib. But the recurrence has occurred since 4 years ago. The several drugs such as high- dose imatinib, Sunitinib Everolimus, Regorafenib, and surgery have been applied but the disease progressed. Several masses in the abdomen and pelvis that were inoperable caused discomfort and pain. The skin covering the tumor appeared normal. The patient had local and radicular pain in the affected area that interfered with her normal function. The patient's right thigh was numb. Due to the size of the mass and its adhesion to the intestine, surgery was not possible. Because of the risks of the reirradiation procedure, we decided to test the usefulness of LVHF ECT in reducing patient disability. These treatment sessions were conducted at Bu Ali Hospital in Tehran, under approval by the Human Research Ethics Committee of Baqiyatallah University (IRCTID: IRCT20230403057807N1).

2.Treatment protocol

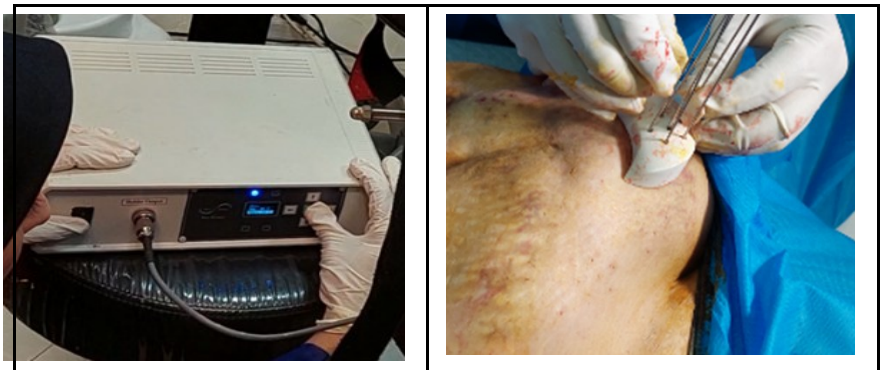
After signing the informed consent form, 3 electrochemotherapy sessions were prescribed for the patient. In each session, the chemotherapy drug containing 30 mg of bleomycin diluted with 100 ml of normal saline was injected intravenously for 10 minutes. Ten minutes after the injection, in the presence of an anesthesiologist, the patient was unconscious, and the applicator was placed in the tumor site with six 20 cm electrodes (one negative electrode and 5 positive electrodes) made in PersianTarava company's laboratory, Tehran, Iran, were directly inserted into the tumor tissue.

A series of 4000 square pulses with an amplitude of 70 V/cm and a frequency of 5 kHz was applied inside the tumor using an electrochemotherapy device designed and manufactured by Persian Trava company (Fig. 1).

The tumor volume was calculated from the main diameter (a) and the longest diameter perpendicular to the main diameter (b), according to the formula $V=\pi ab^2/6$ (15).

3. Results

The patient did not have a fever after treatment. After two weeks, the tumor volume reached 79% of the initial volume and the treatment was repeated (session 2). After 4 weeks, the tumor volume reached 66% and the treatment was repeated (session 3). After 6 weeks, the tumor volume reached 51% (Table 1). The numbness of the patient's right thigh was removed. It was intuitively observed that the tumor tissue became softer than before. After the completion of the electrochemotherapy sessions, the CT image was retaken. By comparing the CT images before and after the treatment, it was determined that the tumor was not separated from the intestine and it was not possible to remove the mass with surgery. It was observed that the relative increase of the tumor volume after the third session compared to before the start of treatment is 51%. According to the WHO guidelines, it is considered a partial response (PR).

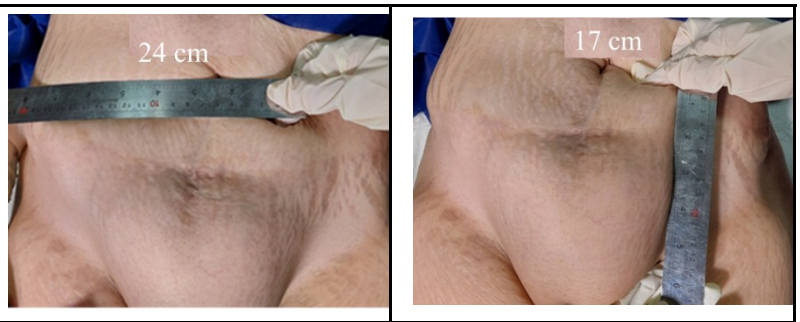


(a) (b)

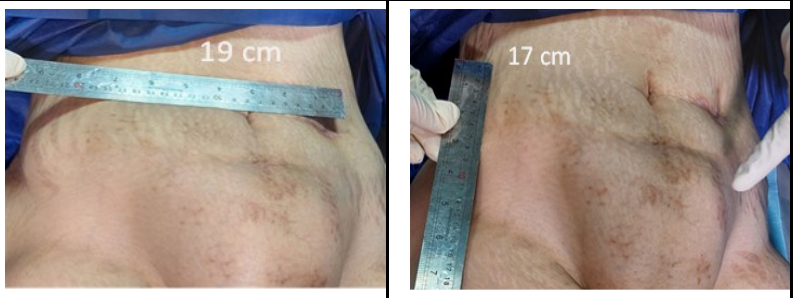
Figure 1. a) Persian Tarava electrochemotherapy device. b) Arranging the electrodes on the tumor with the help of the applicator.

Table 1: Tumor volume

Section	a diameter (cm)	b diameter (cm)	Volume (cm^3)	Normal volume% (V/V_0)
1 Initial volume of tumor (V_0)	24	17	3629.84	100
2	19	17	2873.62	79
3	18	16	2411.52	66
Final volume	18	14	1846.32	51



Before treatment



The tumor 2 week after the first LVHF ECT session

The tumor 4 week after the first LVHF ECT session

Figure 2. The length and width of the tumor, measuring with a ruler.

4. Discussion

Electrochemotherapy is a local ablative treatment for reversible electroporation and intracellular accumulation of hydrophilic drug molecules, greatly increasing their cytotoxicity. This method is combined with other treatment methods or alone for tumors that cannot be operated (16).

The mechanism of electroporation is that when an external electric field is applied, it induces a transient potential by redistributing ions across the lipid bilayer. When this potential exceeds a critical threshold (approximately 0.2-1 V, depending on the cell type), the phospholipid bilayer becomes unstable, leading to localized structural defects. As a result, ions and other macromolecules can penetrate the cell membrane as a result of structural defects in the phospholipid bilayer (17). The pore formation process is as follows: the forces induced by the electric field polarize the water molecules and lipid groups, creating initially hydrophobic pores. These pores transform into hydrophilic pores (1-10 nm in diameter) as the lipid heads reorient towards the aqueous channel. The pores remain for a few milliseconds to minutes after the pulse, which is influenced by the pulse duration and membrane composition (18).

The present study is a case study for the treatment of a tumor on the abdomen caused by the metastasis of GI cancer, which could not be surgically removed due to the large size of the tumor and its connection to the intestine. The advantages of using ECT in the treatment of solid tumors certainly lie in the fact that it is cheap and easy to perform.

In addition, systemic side effects are few, so it can be used in elderly patients or those who are in poor physical condition (19). Rega et al. (2022) reported on three patients with locally advanced rectal cancer (LARC) treated with Standard ECT (low frequency and high voltage). The results showed that in two patients, the disease was stable after ECT, while one patient achieved a complete response. For each patient, pain relief was observed. They concluded that ECT is a safe and effective treatment, allowing for pain relief and thus improved quality of life (20). However, its effectiveness is reduced for tumors with a diameter of 3 cm or more (21). The reasons for reduced efficacy in larger tumors are not fully understood, but may be related to challenges in achieving adequate electroporation and drug delivery across the entire tumor volume (22-24). Standard operating procedures for ECT may need to be modified for the treatment of large tumors, potentially involving multiple treatment cycles or advanced treatment planning. In ECT with a traditional protocol, low-frequency pulses (LF-ECT) are used for treatment, which uses higher-frequency, lower-voltage electroporation to reduce muscle contractions and pain associated with traditional treatment (25) Therefore, in the studies we have done to increase the permeability of cancer cells, we used a pulse with a low electric field with high repetition (22-24). The optimal protocol used after conducting preclinical research (26 -30). A series of 4000 square pulses with an amplitude of 70 V/cm and a frequency of 5 kHz was applied. In this study, after 3 sessions of large tumor treatment, in which bleomycin was injected intravenously, according to the WHO guidelines, a partial response in the tumor size and a reduction in the patient's discomfort was observed. Lyons et al. (25) evaluated high-frequency electrochemotherapy treatment in 97 lesions in 25 patients. At 12 weeks after treatment, 79% had a complete response and 12.3% had a partial response. They showed that HF-EP with chemotherapy showed promising results in terms of tumor response rates for cutaneous malignancies of different histological subtypes compared with traditional ECT protocols. The results of our study are consistent with those of Lyons et al. (25). In addition, the results could be promising in terms of effectiveness in improving the quality of life of patients by reducing pain. The limitations of this study were related to the sample size. These results need to be confirmed on a larger group of patients because the results reported in this manuscript are only an experience at a single cancer center. After treating a sufficient number of patients, the preclinical phase will be completed. Then, like in European hospitals, this treatment method will be used in Iranian hospitals as an adjuvant treatment.

5. Acknowledgment

The authors acknowledge financial support from the cancer research center of Bu Ali hospital, Tehran, Iran.

6. Conflict of Interest

The authors declare no Conflict of interest.

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