Effective Treatment of Cervical Lymph Node Metastasis of Breast Cancer by Low Voltage High-Frequency Electrochemotherapy

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Abstract- Electrochemotherapy (ECT) is a new local treatment method for solid and superficial tumors. During this new technique, patients experience an unpleasant sensation and slight edema. Most unpleasant and painful is mainly attributed to muscle contractions provoked by high amplitude and low repetition frequency pulses. Recently, we showed that electrochemotherapy using low voltage and higher repetition frequency (LVHF ECT) is an effective tool for inhibiting tumor growth and inducing cell permeabilization. Low voltage high-frequency electrochemotherapy was developed and optimized in vitro and in vivo which and can be used in the clinic. In the present study, we report a case of cervical lymph node metastasis of breast cancer treated by the technique**.** In our case, LVHF ECT was successful in reducing the size and palliating the symptoms of cervical lymph node metastasis in clinical conditions, whereas other approaches were inefficient. Our electrochemotherapy technique shows good clinical results. However, more studies on this new method are necessary to prove that LVHF ECT can be considered as a standard treatment modality.

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Introduction

Standard Electrochemotherapy (ECT) is a new cancer treatment technique which used high-intensity electrical by low-frequency pulses to damage the cell membrane reversibly and so increase the entrance of cytotoxic chemotherapy drugs into tumor cells (1). Electrochemotherapy with bleomycin or cisplatin as non-permeant chemotherapy drugs has been successfully used in different solid and superficial tumors (2-4). The standard ECT protocol uses a train of high-amplitude, rectangular pulses with 1-Hz repetition frequency (5). By this protocol, patients experience an unpleasant sensation and slight edema or erythema at the site of electrical pulses. Most unpleasant and painful, according to the patients, are the sensations during the pulse delivery, which are mainly attributed to muscle contractions provoked by high-amplitude and low-frequency pulses. Edema results from high local current density (4,6,7). In order to reduce the pain sensation during ECT, application of a high-frequency or low-amplitude electric field has been suggested (6-9). In our previous studies, we used low electric field pulse with high repetition frequency for permeabilization of cells and treatment of mice tumors. The results showed that this technique was at least as effective as standard procedure with more acceptable side effects (10-13).

There is a large body of evidence that shows ECT is effective to treat cutaneous and subcutaneous tumors of any kind in human. Superficial metastasis of malignancies such as head and neck squamous cell carcinoma, malignant melanoma, basal cell carcinoma, adenocarcinoma of the breast and salivary gland, hypernephroma, Kaposi sarcoma and transitional cell carcinoma of the bladder were palliated effectively by the technique with reported response rates of 48-100%

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(14,15). Responses to ECT are significantly dependent on tumor characteristics such as type, size, firmness, location and also treatment protocol. Better responses were seen in smaller tumors for coverage of the whole nodule was easy. For some larger nodules, repeated procedures were needed (16,17).

Here, we report a case of metastatic breast cancer to the cervical lymph node in which LVHF ECT has proven useful in reducing the size of the metastatic nodule and palliate the patient's symptoms.

Case Report

A 44-year-old woman with a history of right breast cancer for 3 years was admitted to our clinical oncology department in Shohada-e-Tajrish Hospital, Tehran, Iran. Her primary treatment had been Modified Radical Mastectomy then adjuvant chemotherapy and radiation therapy to the right chest wall and supraclavicular area. The primary tumor was T3N2M0 and receptor status was ER-, PR- and Her2neu-. During follow-up, a right lower cervical lymphadenopathy was developed, and metastasis from breast cancer was proved by needle biopsy. IHC on the biopsy specimen showed that receptor status was ER-, PR- and Her2neu+. No other visceral or bone metastasis were established by imaging except a small nodule in the liver suggestive for metastasis but was not biopsied. Then she received one line of palliative chemotherapy combined with Herceptin, and the cervical nodule got a bit smaller and after treatment stopped again progressed. On physical examination, there was a firm and tender, low cervical mass on the right side that was fixed to surrounding tissues. The external dimensions of the mass as measured by a ruler were 6 cm and 5 cm. The overlying skin seemed normal. The patient had a disturbing local and radicular pain in involved area that interfered with her normal function. Because of the risks of reirradiation, we decided to test the usefulness of LVHF ECT to reduce the patient's disability.

Treatment protocol

After signing the informed consent form, the patient was treated. The chemotherapy consisted of 30 mg Bleomycin diluted with 200 ml normal saline and infused over 20 minutes intravenously. Ten minutes after the infusion, with local anesthesia and sterile technique, electric pulses were applied to the tumor using an ECT-SBDC (designed and made in the Small Business Development Center and Electromagnetic Laboratory of the Medical Physics Department of Tarbiat Modares University, Tehran, Iran). A needle electrode-hexagonal array (length, 16 mm) was inserted directly into the tumor mass (made in the Laboratory of the mechanic Department of Tarbiat Modares University, Tehran, Iran). The tumor volume was calculated from the major diameter (a) and the next longer diameter perpendicular to a (b), according to the formula $V=\pi ab^2/6$ (Table 1). Eight minutes after injection, therapy was begun with using an ultrasound guided. A series of 4000 pulses of 70 V/cm was delivered at a frequency of 5 kHz and duration of 100 microseconds. The patient had no residual pain, fever, or discomfort after the treatment. After two weeks, the tumor volume was reached to 47% of the initial volume (Figure 2). We repeated our treatment after 3 weeks. At this time, the tumor volume was reduced to 24% of the initial volume (Figure 3) and two months after treatment; the lesion was not grown (Table 1).

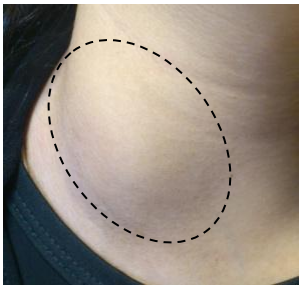

Figure 1. Before treatment, there was a firm and tender, low cervical mass on the right side that was fixed to surrounding tissues. The external dimensions of the mass were 6 cm and 5 cm.

Figure 2. The tumor 1 week after the first LVHF ECT session

Figure 3. The tumor 1 week after the second LVHF ECT session.

Table 1.Tumor volume

	a diameter (cm)	b diameter (cm)	Volume (cm^3)	Normal volume% (V/V0)
Initial volum (v0)	5	6	75	100
Tumor volume after 1 week	4	5	40	53.33
Tumor volume after 2 weeks	3.5	4.5	27.56	36.74
Tumor volume after 1 month	3	4	18	24.00
Tumor volume after 3 months	3	4	18	24.00

Discussion

Standard electrochemotherapy has been demonstrated to be an effective treatment method for solid tumors in clinical approaches. In several clinical experiments, ECT with bleomycin as a non-permeant highly cytotoxic and inexpensive chemotherapy drug gave the best response rates in superficial tumors (18-20). Despite the benefits of this approach, some side effects were reported. The most unpleasant and painful side effects of ECT have been reported are muscle contractions and related sensations during pulse delivery (4,6,7). It would be possible to reduce these painful sensations using pulse frequencies higher than tetanic contractions or lower electric field strength (6-9,21). The clinical disadvantage of ECT with the standard protocol is using high voltage pulses for treatment. Therefore, we used low electric field pulse with high repetition frequency for permeabilization of cancer cells (22-24) for the treatment of mice tumors (10-13,25) and optimized our suggested ECT methods for clinical trials. Among treatment groups, the system gives the optimal permeabilization when we used a train of 4000 square pulses with 70 V/cm amplitude and at 5 kHz frequencies. After preclinical researches, we decided to use LVHF ECT with bleomycin in our patient to reduce the tumor volume and patient's discomfort. LVHF ECT in our case showed the successful result in local control and volume reduction of the metastatic lymph node in clinical condition, whereas other approaches, such as chemotherapy, radiotherapy, and surgery have been inefficient and hazardous. The response rate of LVHF ECT which observed in the present study is similar to results obtained in the standard ECT. In previous studies, researchers demonstrated that standard ECT was more effective in tumors smaller than 3 cm in diameter (14,16,17). Therefore, we can expect complete responses in smaller tumors. Unlike traditional chemotherapy protocols, the treatment response occurred without any morbidity for the patient, and with safe conditions due to the minimal doses of bleomycin, local anesthesia, the absence of surgical wounds, and risk of ionized radiation. In Standard ECT protocols, general anesthesia is used when a big nodule is treated, but we used LVHF ECT in the treatment of a big and firm tumor with local anesthesia, and it was tolerable for the patient (14,16,17). Despite unsatisfactory results of the treatment, our present protocol was comfortable and tolerable for the patient.

We suggest that LVHF ECT can be an effective, safe and tolerable treatment technique for superficial tumors without side effects of traditional therapeutic methods. Also, this treatment is repeatable. More studies on this new method are necessary to prove that LVHF ECT can be considered as a standard treatment modality. However, according to positive results of previous and also our studies, LVHF ECT should be considered as a suitable treatment option for situations in which other standard modalities fail to palliate the patients.

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