Electrochemical Treatment of Localized Tumors with Direct Current

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ABSTRACT: To develop cancer electrochemical treatment (ECT) in the United States, we have conducted basic studies and started a Phase I clinical trial. Our in vivo preliminary results indicate that ECT is effective on RIF-1 mouse tumor and rat fibrosarcomas. In the in vitro study ECT clearly demonstrated dose-dependent human oral carcinoma KB cell growth inhibition by colony-forming assay. We have started an animal study to resolve the ECT methodological problems for rat breast cancer. Meanwhile, we began a clinical trial treating patients with recurrent superficial measurable malignant tumors. Our goal is to make ECT a useful alternative method for treating localized tumors.

INTRODUCTION:
Electrochemical treatment (ECT) of cancer has been used for only a few decades. Since Nordenström reported his clinical results [1], this method has been studied in Japan, Slovenia, and China [2,3,4]. Xin [4] modified Nordenström's original method by inserting both cathode and anode platinum electrodes into tumors of conscious patients. A constant voltage of less than 10 V is applied to produce a 40-80 mA current between the anodes and cathodes for 30 minutes to several hours, delivering 100 coulombs per cubic centimeter. Due to electrolysis, electrophoresis, and electroosmosis, cells near the electrodes are killed by the microenvironmental changes [5].

Although a number of clinical studies have shown that ECT has an antitumor effect and has been used as an alternative method for cancer treatment, ECT has not been universally accepted. The reason is that the published data lacks essential preclinical studies, and reliable controlled clinical trial is missing. It is necessary to conduct preclinical studies and clinical trials to verify its value. In this paper, we outline our efforts during the last five years in developing ECT as an alternative cancer treatment at the City of Hope.

DEVELOPMENT:
Office of Alternative Medicine Grant
The ECT study at the City of Hope started in September of 1993 with a seed grant from the National Institute of Health, Office of Alternative Medicine. The specific aims were to conduct an in vivo study to standardize animal experiments, to establish dose-response relationship, and to develop a large scale study proposal. In vivo studies were conducted to evaluate the effectiveness of ECT on animal tumor models and to standardize animal experiments [6]. Radiation-induced fibrosarcomas were subcutaneously implanted in 157 female C3H/HeJ mice. Larger rat fibrosarcomas were implanted on 34 female Fisher 344 rats. When the spheroidal tumors reached 10 mm in the mice, 2-5 platinum electrodes were inserted into the tumors at various spacings and orientations. Ten rats in a pilot group were treated when their ellipsoidal tumors were about 25 mm long; electrode insertion was similar to the later part of the mouse study, i.e., two at the base and two at the center. A second group of 24 rats were treated with 6-7 electrodes when their tumors were about 20 mm long, all electrodes were inserted at the tumor base. Of the 24 rats, twelve of these were treated once, ten treated twice, and two treated thrice. All treated tumors showed necrosis and regression for both mice and rats; however, later tumor recurrence reduced long term survival. When multiple treatments were implemented, the best three-month mouse tumor cure rate was 59.3%, and the best six-month rat tumor cure rate was 75.0%. These preliminary results indicate that ECT is effective on the RIF-1 mouse tumor and rat fibrosarcoma. The effectiveness is dependent on electrode placement and dosage.

In Vitro studies were conducted on human KB oral cancer cells [7], which included: 1) cytotoxicity study exposing cells to different electrical doses, 2) clonogenic assay to study colony-forming abilities of the cells after ECT, 3) thymidine incorporation assay, 4) pH measurement. ECT was found to delay cell growth by using 1.5 coulomb (400 µA x 75 min) in 5 ml of culture medium. ECT clearly demonstrates dose-dependent tumor cell survival by colony-forming assay. Cytotoxicity study by methylene blue assay determined that the median toxic concentration (ID₅₀) value is 3 coulomb (400 µA x 125 min)/5 ml to 2.5 x 10⁶ cells in culture. For a fixed dose (3 coulomb, 400 µA x 125 min/5ml), the higher the current, the less cell kill due to shorter treatment time. Time is, therefore, an important factor. When cell concentration was altered, the survival was higher for increased cell concentrations. Thymidine incorporation assay indicated that ³H thymidine incorporation into DNA decreases as ECT dose increases. At 5 coulomb (400 µA x 125 min)/5
ml, pH at the anode decreased to 4.53 and at the cathode increased to 10.46. These results indicate that ECT is effective for killing human KB cancer cells in culture system and the toxicity effect is related with coulomb, i.e., current and treatment time.

Army Breast Cancer Research Program

The most important specific aim of the Office of Alternative Medicine's seed grant was to develop a large-scale study proposal. Breast cancer is a leading cause of women cancer death. Furthermore, the local regional recurrence following standard treatment is one of the major problems for patients with breast cancer. Effective local control is an unsolved problem. In order to make ECT available for breast cancer patients in the United States, who have failed or cannot bear conventional therapy, we developed a research proposal to resolve the ECT methodological problems for breast cancer. This research proposal, entitled "Electrochemical Treatment of Breast Cancer with Direct Current", is being funded for two years by the Department of Defense Breast Cancer Research Program, USAMRMC (United States Army Medical Research and Matériel Command).

This research project was proposed to resolve the ECT methodological problems. The MTF7 rat breast cancer cell line implanted in Fisher 344 rats' mammary fat pads will be used as a cancer model. We will test the hypothesis that tumor responses are dependent on electrode spacing and treatment dose, and will determine the optimal spacing and dose for treating breast cancers. Morphology of the tumors treated with various electrode spacings and doses will be tested. This morphology study will determine the effective region. Finally, tumor size, local control rate, and rat survival rate with various electrode spacing and doses will be studied. This hypothesis will provide essential information about optimal electrodes spacing and dosage. Division of Anatomic Pathology has participated in this study. The results of this research will help formulate a standardized ECT method for breast cancer treatment and provide a better understanding of ECT mechanisms.

Phase I Clinical Trial

Besides the basic research program, we have also started a clinical trial entitled "Phase I study of electrochemical treatment of recurrent superficial measurable malignant tumors." A clinical protocol was submitted to the institutional review board (IRB) at the City of Hope in June 1995. For more than a year, the clinical protocol was reviewed and revised many times. Safety was the main concern since this treatment has not been reported in the United States. According to an FDA investigational device exemption (IDE) regulation, ECT was considered as a significant risk device. Therefore, an application to FDA was submitted in April 1996, and an approval was granted in July 1996. This protocol was approved by the IRB in September 1996. The first patient treatment took place on October 3, 1996.

The Phase I trial asks for 25 recurrent superficial measurable malignant tumors treatment. The purposes of these clinical trials are to evaluate ECT tumor response and record the acute and late ECT toxicities in the treatment of superficial tumors. Five late stage patients have been treated as of July 1997. Three patients developed complete response, one partial response, and one no response (tumor reduced less than 50%) due to incomplete treatment. All patients tolerated treatment well.

CONCLUSIONS:

During the past five years, ECT has been developing at the City of Hope. Our preliminary In Vitro and In Vivo studies indicated that ECT is an effective tumor treatment. It confirmed the results reported in other studies, and through these efforts, we were able to start ECT clinical trials in the United States. It could be expected that our research program, including basic researches and clinical trials, will help formulate a standardized ECT method for cancer treatment and provide a better understanding of ECT mechanisms. The goal of this research is to make ECT a useful alternative method for treating localized tumors.

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REFERENCES: