

case report

Electrochemotherapy with cisplatin of breast cancer tumor nodules in a male patient

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Background. The metastases of breast cancer in a male patient were treated with electrochemotherapy by intratumoral injection of cisplatin. Electrochemotherapy is chemotherapy with the subsequent local application of electric pulses to the tumor nodules in order to increase drug delivery into the cells.

Case report. Cutaneous metastases of breast cancer were treated with the intratumoral administration of cisplatin and by 8 electric pulses (1300 V/cm) applied a minute later to each cutaneous metastasis. The treatment resulted in complete response of two electrochemotherapy treated cutaneous metastases and partial response of the third metastasis. In cutaneous metastases treated with intratumoral administration of cisplatin without electric pulses, only partial response was obtained.

Conclusion. This study confirms that electrochemotherapy with cisplatin is effective in the treatment of breast cancer metastases, too, as it was already proved for electrochemotherapy with bleomycin.

Key words: breast neoplasms, male - therapy - drug therapy; cisplatin; electroporation; drug delivery system, electrochemotherapy

Introduction

Electrochemotherapy is a treatment approach that utilizes the application of electric pulses to tumors in order to facilitate the accumulation of chemotherapeutic drugs in the cells.¹ In preclinical studies, it was demonstrated *in*

vitro and *in vivo* that cytotoxicity and antitumor effectiveness of bleomycin and cisplatin is potentiated several fold by electrochemotherapy.²

These favorable preclinical data have been confirmed in the clinical studies on cancer patients with cutaneous and subcutaneous tumors treated by electrochemotherapy with bleomycin and with cisplatin.³ Objective responses were obtained for the majority of the electrochemotherapy - treated lesions, whereas the lesions that were only exposed to electric pulses or only treated with bleomycin or cisplatin did not respond.

Electrochemotherapy with cisplatin, given

Received 22 June 2000

Accepted 8 August 2000

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intratumorally, was demonstrated to be effective on many different tumor types, but not on breast cancer metastases.^{4,5} Therefore, the aim of this study was to determine whether electrochemotherapy with cisplatin would also be effective in the treatment of cutaneous metastases of breast cancer.

Case report

Patients' history

A male patient, born in 1932 (H.F. No.: 6804/90) has been treated for locally advanced right breast cancer since 1990. He received 4 cycles of chemotherapy, consisting of epirubicin, cyclophosphamide and 5-FU and was also irradiated to the right mammary region. Clinically, complete remission was achieved, but it was never histologically proved. He was then treated with hormonal therapy with tamoxifen until the first progression of disease in July 1997 with lung metastases and locoregional progress in the right mammary region. After the progress, the patient was treated with the second and third line hormonal therapy with aminoglutethimide and anastrozole. Both treatments resulted in stagnation of lung and cutaneous metastases and lasted approximately 1 year. In July 1999, the second line chemotherapy with etoposide was started due to the progression of lung metastases. With chemotherapy, the stagnation of lung metastases was achieved only until November 1999 when the lung and cutaneous metastases in the right mammary region progressed again. We started to apply electrochemotherapy to the cutaneous metastases in right mammary region; the possibilities of standard treatment were tired out.

Electrochemotherapy protocol

Electrochemotherapy consisted of intratumoral administration of cisplatin and subsequent exposure of cutaneous breast cancer

nodules to electric pulses. Cisplatin was administered intratumorally, at a dose of 1 mg per 100 mm³ of nodule. The time interval between the cisplatin administration and of electric pulses application was 1 minute. The nodules to be treated were sprayed with Xylocaine in order to avoid pain. Square wave electric pulses of 100 μ s, 910 V amplitude (1300 V/cm), frequency 1 Hz were delivered through two parallel stainless steel electrodes (distance 7 mm, width 7 mm, length 14 mm, with rounded tips) with an electropulsator Jouan GHT 1287 (Jouan, France). Electric parameters were controlled by oscilloscope HM 205-3 (Hameg Instruments, Germany). Electric pulses were delivered in two trains of 4 pulses with one-second interval, in two perpendicular directions (4+4 configuration). A good contact between electrodes and the skin was assured by means of conductive gel. When several nodules were treated at the same time (in the same session), electric pulses were delivered one after the other at the intervals of at least 1 minute.

Follow up

During electrochemotherapy, the patient was monitored for the evaluation of acute treatment side effects. Immediately after the therapy, the patient remained in the outpatient clinic for two hours before he was released home. The patient was examined in two-week intervals for the evaluation of response to electrochemotherapy. Tumor nodules were measured with calliper and photographed before and after treatment.

According to WHO guidelines, the response to electrochemotherapy was assessed as complete response (CR), if nodules became impalpable, partial response (PR), if nodules decreased in size by more than 50%, no change (NC), if they decreased in size by less than 50% or increased in size by less than 25%, and progressive disease (PD), if they increased in size by more than 25%.

Results of the treatment

In November 1999, the patient agreed to enter the electrochemotherapy protocol. Three of 10 cutaneous metastases, one on the right shoulder and two in the right mammary region, were treated with electrochemotherapy. Two cutaneous metastases in right mammary region were treated with intratumoral administration of cisplatin without electric pulses. Five cutaneous metastases served as controls (Table 1).

Eight weeks later, CR was obtained in two metastases treated with electrochemotherapy, and PR was obtained in the third metastasis (Figure 1). In both metastases treated with intratumoral administration of cisplatin without electric pulses, partial response was obtained 8 weeks later (Figure 2). Three of control metastases progressed, and two of them were the same size.

Six months after the beginning of treatment, in May 2000, another progress of disease in the lung was found and the patient died due to lung metastases at the end of the same month. The two metastases in which CR was achieved with electrochemotherapy, remained in CR until the patient's death, whereas the third metastasis in which only PR was achieved has already progressed by that time.

Electrochemotherapy was well tolerated by the patient. There were no major local or general side effects. The intratumoral route of cis-

platin was tolerable, the patient did not complain of the pain. The application of electric pulses induced muscle contractions beneath the site of treatment after each pulse, but they were released immediately after the pulse was discontinued. After the treatment, only erythema and slight oedema occurred at the treated area, but both disappeared in one day. There were no exulcerations of cutaneous nodules. After electrochemotherapy, the patient did not complain of fatigue or other kind of discomfort. The treatment with intratumoral cisplatin did not cause any local or systemic toxicity.

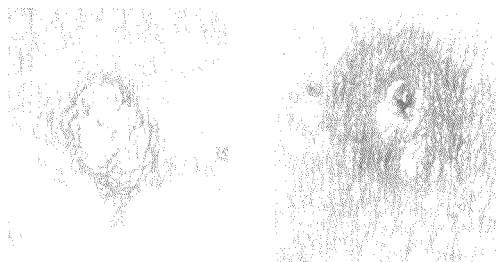
Discussion

This case report shows that electrochemotherapy is effective also in the treatment of cutaneous breast cancer nodules, because in two electrochemotherapy treated cutaneous nodules CR was obtained and, in the third nodule, PR was obtained.

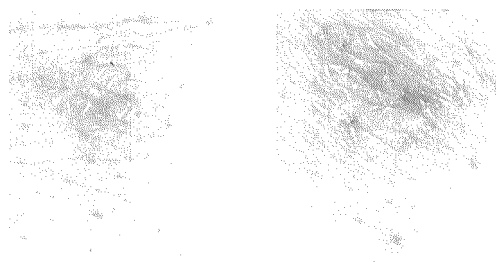
Electrochemotherapy was already proved to be effective in the treatment of cutaneous and subcutaneous nodules of different histological types of tumors. Mostly used chemotherapeutic drugs were bleomycin and cisplatin. The results of numerous trials performed at five cancer centers demonstrated that electrochemotherapy with bleomycin is very effective in the treatment of cutaneous

Table 1. Summary of tumor response

Treatment	Size of the treated nodules (mm ³)		Response
	Before treatment	After 8 weeks	
Control nodules	417.8	2436.3	PD
	9.4	10.6	NC
	10.5	13.0	NC
	34.5	57.6	PD
	22.0	41.9	PD
Cisplatin	37.7	18.3	PR
	20.1	7.8	PR
Electrochemotherapy	37.7	0	CR
	30.2	0	CR
	13.9	3.1	PR



A **B**
Figure 1. Photomicrograph of tumor nodule before electrochemotherapy (A) and 8 weeks after it (B). The nodule ($V = 37.7 \text{ mm}^3$) was injected with 0.377 mg of cisplatin and, after 1-minute, 8 electric pulses (1300 V/cm, 1 Hz, 100 s) were applied to the nodule. Eight weeks after the treatment, the tumor nodule was in CR.



A **B**
Figure 2. Photomicrograph of tumor nodule before treatment with cisplatin (A) and 8 weeks after it (B). The nodule ($V = 37.7 \text{ mm}^3$) was injected with 0.377 mg of cisplatin intratumorally. Eight weeks after the treatment, the tumor nodule was in PR.

and subcutaneous nodules of different tumors, including breast adenocarcinoma nodules.⁶ In all of the nodules CR was obtained. Eight additional metastatic breast cancer nodules were treated with electrochemotherapy; but they couldn't be evaluated because the follow-up was too short.

The first clinical study of electrochemotherapy was performed at the Institute of Oncology, Ljubljana, by evaluating antitumor effectiveness of electrochemotherapy with intratumorally administered cisplatin. In all electrochemotherapy treated nodules of histological different tumors, CR was obtained.⁴ Another clinical study on malignant mela-

noma patients showed that electrochemotherapy with intratumoral administration of cisplatin is effective, resulting in 68% of CR in the treated cutaneous tumor nodules.⁵

No clinical study on electrochemotherapy of cutaneous breast cancer nodules with cisplatin administered intratumorally has been done so far. Some preclinical studies were made on electrochemotherapy and intramuscular administration of bleomycin to breast cancer nodules in experimental animals.⁷ Thirty-three of 38 electrochemotherapy treated nodules regressed at least partially within 2-3 weeks, three of them were cured. In none of the control nodules treated only with bleomycin given intramuscularly neither partial response nor growth arrest were attained.

In conclusion, clinical studies of electrochemotherapy with cisplatin administered intratumorally have demonstrated to be effective and safe in the treatment of different histological types of tumors. Our case report demonstrates it is effective in the treatment of breast cancer nodules, too. The clinical study on more breast cancer patients is going on.

Acknowledgement

This work was funded by research grant from the Ministry of Science and Technology of the Republic of Slovenia and in part by IGEA s.r.l. Carpi (Modena) Italy.

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