Electrochemotherapy with cisplatin of cutaneous tumor lesions in breast cancer

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We have evaluated the efficiency of electrochemotherapy with cisplatin on cutaneous tumor lesions of breast cancer and have compared its efficiency with the efficiency of intratumoral (i.t.) administration of cisplatin alone. The study was performed on six breast cancer patients with 26 cutaneous lesions in whom all standard treatment modalities were exhausted. Of 26 lesions, 12 were treated by electrochemotherapy, six by i.t. cisplatin application, while eight were controls. In all 12 lesions treated by electrochemotherapy and followed-up for up to 26 weeks at the most, the objective response was obtained [complete response in 33% with mean duration of 10 weeks and partial response (PR) in 67% with a mean duration of 5 weeks]. In six lesions treated with i.t. application of cisplatin and followed-up for up to 12 weeks at the most, objective response was obtained in 83% of lesions; none of these responses were complete, the mean duration of PR was 5 weeks. During electrochemotherapy, only minimal local side-effects were observed, whereas no systemic side-effects of the treatment were noticed. We conclude that electrochemotherapy with i.t. cisplatin application is effective in local treatment of cutaneous tumor lesions of breast cancer. *Anti-Cancer Drugs* 15:593–597 © 2004 Lippincott Williams & Wilkins.

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Introduction

Due to very slow or impeded transfer of many chemotherapeutics through the cell membrane, cytotoxicity of these agents is considerably reduced. In order to obtain a satisfactory concentration of the drug in the cell, high doses of chemotherapeutic need to be delivered in systemic treatment, which may result in undesirable side-effects. There are several methods to increase the drug concentration in the cell. One of them is electroporation, which applies direct current electric pulses to the tumor lesions to increase membrane permeability [1]. Treatment with electric pulses and chemotherapy is called 'electrochemotherapy'. In preclinical studies, it was demonstrated that electrochemotherapy is a very effective treatment resulting in tumor cures at chemotherapeutic drug doses that have no antitumor effect on their own [1–3].

Clinical studies on electrochemotherapy have been performed most frequently on patients with advanced metastatic cancer in whom possibilities of standard treatment were exhausted. The patients included into these studies were mainly treated for malignant melanoma, basal cell carcinoma, squamous cell carcinoma, and a few individual patients with adenocarcinoma and Kaposi's sarcoma [4–14]. The study performed on s.c. tumor lesions of the patients with clear-cell adenocarcinoma of the kidney demonstrated that this treatment is also effective for cancer that is generally resistant to systemic chemotherapy [11]. The chemotherapeutics that were applied in the above clinical studies were bleomycin and cisplatin [4–14]. Electrochemotherapy with the intratumoral (i.t.) administration of bleomycin or cisplatin yielded a higher percentage of complete responses (CRs) than i.v. administration of these two drugs. In electrochemotherapy with i.v. and i.t. administration of bleomycin, CR was obtained in 17 and 50% of patients, respectively. In electrochemotherapy with i.v. and i.t. administration of cisplatin, CR was obtained in 11 and 74% of patients, respectively [4–14].

So far, only a few reports on electrochemotherapy of cutaneous tumor lesions of breast cancer have been published in the medical literature. In the research center in Tampa (USA), a CR was obtained by electrochemotherapy with i.v. administration of bleomycin in two cutaneous tumor lesions of breast cancer, whereas in the research center in Mexico City (Mexico), in the treatment of 14 cutaneous tumor lesions by electrochemotherapy with i.t. administration of bleomycin, CR was obtained in 58% of the lesions and partial response (PR) in 42% of the lesions [5,12]. To date, no clinical

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study on electrochemotherapy with cisplatin has been carried out on breast cancer patients. Considering our experience with the effectiveness of electrochemotherapy with cisplatin in the treatment of some cancers, we decided to assess its effectiveness also in the treatment of breast cancer. The aim of our study was to evaluate the antitumor effectiveness of electrochemotherapy with i.t. administration of cisplatin in the treatment of cutaneous tumor lesions of breast cancer and to compare it to the effectiveness of treatment with i.t. administration of cisplatin alone.

Patients and methods

Patients

From October 1999 to March 2002, six patients with histologically confirmed breast cancer were included in the study. The patients had metastatic breast cancer with measurable cutaneous nodules and had received prior standard treatment (surgery, chemotherapy, hormonal therapy or radiotherapy) or refused other standard treatments. The study was approved by the Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia. Before the start of the therapy, each patient signed an informed consent form notifying that they consented to the suggested treatment modality.

The set of inclusion criteria involved the following: metastatic breast cancer, the exhausted possibilities of standard treatment, age >18 years, at least one measurable cutaneous or s.c. tumor lesion, no local therapy applied to the site of the lesion in the last 4 weeks, no irradiation of this site in the last 8 weeks, normal blood count (neutrophils $>1.5\times10^9$/l, Hb >100 g/l, thrombocytes $>100\times10^9$/l), adequate liver function (AST and ALT up to 5 times the normal value, total bilirubin up to 1.5 times the normal value), adequate renal function (creatinine clearance above 60 ml/min), at least 2 weeks from the previous systemic therapy.

Before the therapy, all patients underwent clinical examination and the following laboratory tests: full blood count with differential blood count, and the measurements of the content of sodium, potassium, chlorine, phosphate, magnesium, urea, creatinine, bilirubin, AST, ALT, AF, γ-GT, LDH and creatinine clearance. ECG was also performed, and the tumor lesions selected for treatment were measured and photographed.

Methods

The course of treatment was as follows: after local anesthesia by spraying the site of tumor lesion with lidocaine, cisplatin at a concentration of 2 mg/ml of distilled water was administered (Platamine; Pharmacia & Upjohn, Milan, Italy) i.t. in a dose of 1 mg/100 mm^3 of tumor lesion. The volume of tumor lesion was calculated according to the following formula $V=a\times b\times c\pi/6$ (where a, b and c denote the diameters of tumor lesion). At 1–2 min after the administration of cisplatin, we applied square wave electric pulses locally on cutaneous tumor lesions using two superficial plate electrodes (thickness 1 mm, width 7 mm, length 14 mm, inner distance between them 7 mm). Good contact between the electrodes and the skin was assured by conductive gel. Each lesion was treated with eight pulses, divided into four pulses plus four subsequent pulses delivered perpendicularly to the first four pulses. Electric pulses of amplitude 910 V, duration 100 μs and frequency 1 Hz were generated by the electroporator GHT 1287 (Jouan, France). If the lesion was wider than 7 mm, the treatment was performed in several runs of electric pulses with repositioning of the electrodes so that the whole surface of the lesion was exposed to electric pulses. The patients were treated in the outpatient department. Their clinical status was controlled during each treatment session and also 30 min after the session was completed. Patients were usually retained in the hospital for another 2 h to be under observation and were released after final check-up. All patients were then followed-up on an outpatient basis in order to assess the treatment effect and side-effects.

The size of tumor lesions was measured with a caliper. Before applying electrochemotherapy and after its completion, each lesion was photographed. The treatment response was evaluated 4 weeks after the treatment according to WHO classification, in which CR is defined as absence of any trace of the lesion, PR is defined as more than 50% reduction of the lesion, no change (NC) is defined as less than 50% reduction of the lesion and less than 25% enlargement, and progressive disease (PD) if the lesion enlarged by more than 25%.

In CR and PR, the duration of response to treatment was regarded as the time interval from the date when CR or PR was first recorded to the date of tumor progression. Statistical difference between the treatment efficiency of electrochemotherapy and that of i.t. cisplatin administration alone was calculated by the χ^2-test.

Results

Five female patients and one male patient with a total of 26 cutaneous tumor lesions were included into the study. We treated 12 lesions with electrochemotherapy and six with i.t. cisplatin administration alone, whereas eight were controls.

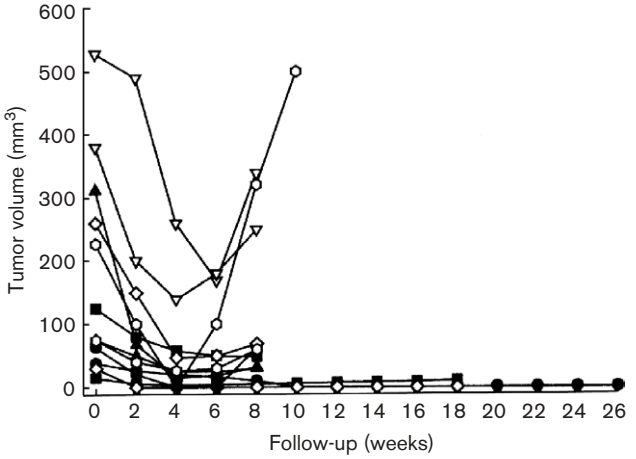
Response to treatment

In all 12 lesions treated by electrochemotherapy and followed-up for up to 26 weeks at the most, objective response was obtained. In four of 12 lesions (33%), CR was obtained; the median duration of CR was 10 weeks. In eight of 12 lesions (67%), PR was acquired

Table 1 Response of tumor lesions to the treatment by electrochemotherapy compared to the response of the lesions treated by i.t. cisplatin administration alone

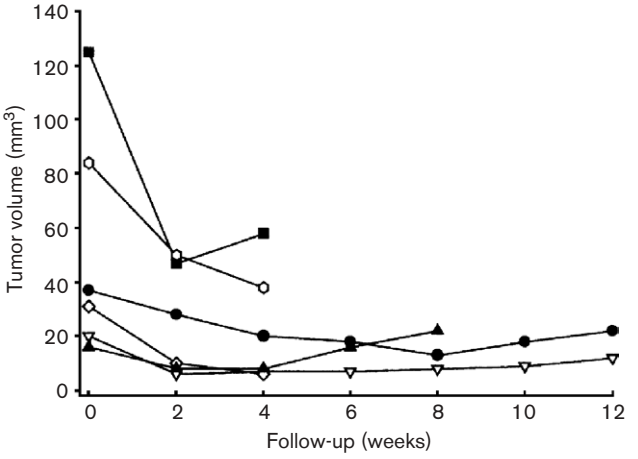
Treatment	No. of lesions	Response to treatment [*n* (%)]					Mean response duration (weeks)	
		OR	CR	PR	NC	PD	CR	PR
Electrochemotherapy	12	12 (100)	4 (33)	8 (67)	0 (0)	0 (0)	10 (4–16)	5 (2–18)
Cisplatin i.t	6	5 (83)	0	5 (83)	1 (17)	0 (0)	–	5 (2–10)

Fig. 1



Efficiency of treatment by electrochemotherapy. Tumor lesions were injected with cisplatin i.t. and immediately thereafter exposed to electric pulses. Antitumor effectiveness was evaluated by measuring tumor diameters and calculating tumor volumes. Tumor lesions were followed-up for up to 26 weeks at the most.

Fig. 2



Efficiency of treatment by i.t. cisplatin administration alone (without electric pulses). Antitumor effectiveness was evaluated by measuring tumor diameters and calculating tumor volumes. Tumor lesions were followed-up for up to 12 weeks at the most.

and the median duration of PR was 5 weeks. Mean volume of the lesions that acquired CR was 72 mm^3 and of those with PR was 192 mm^3 before treatment (Table 1 and Fig. 1).

In six lesions that were treated by i.t. administration of cisplatin, the observation time was up to 12 weeks at the most. In five of six lesions, PR was acquired; its average duration was 5 weeks. In one of six lesions, further progression (PD) was observed. Mean volume of the lesions that acquired PR was 73 mm^3 before treatment (Table 1 and Fig. 2).

Eight tumor lesions served as controls; in six of eight lesions, progression was recorded within the observation period of 9 weeks. In two control lesions, no progress was observed at the death of the patients, i.e. after the observation period of 4 and 10 weeks, respectively.

Statistically significant differences between treatment efficiency (percentage of objective responses) of electrochemotherapy and i.t. administration of cisplatin were not confirmed ($p = 0.261$).

Side-effects of treatment

The patients tolerated electrochemotherapy with cisplatin well. During the application of electric pulses on tumor lesions, all patients complained of muscle spasms in the treated area that were relieved as soon as the delivery of electric pulses was discontinued. In all patients, erythema and edema developed at the site of treatment to which electric pulses were delivered, but they disappeared until the next follow-up appointment, i.e. within the period of 2–4 weeks. On the first follow-up appointment, in all of the patients, the site of the application of electrochemotherapy was covered with a crust with reddish margin all around that persisted for 4–10 weeks after the completed therapy. Two patients with seven lesions complained of itching at the areas covered with crust. In one patient, the skin at the treated site was itchy for 4 days and, in the other, for 7 days after the completed electrochemotherapy. Among the late local toxic effects of the treatment, minimal scarring and depigmentation of

skin were observed on the treated site, and persisted throughout the observation period. No early or late systemic side-effects were observed in our patients.

Discussion

The results of this study showed that electrochemotherapy with i.t. administration of cisplatin is an effective local treatment of cutaneous tumor lesions of breast cancer. In all 12 lesions that were followed-up for up to 26 weeks at the most, objective response to treatment was obtained. In 33%, the response to treatment was CR and lasted on average for 10 weeks. Treatment of lesions by i.t. cisplatin administration alone resulted in no CR, whereas PR was observed in 83% of lesions with a mean duration of 5 weeks.

In our study, there was no statistically significant difference between the treatments by electrochemotherapy with i.t. cisplatin administration and i.t. cisplatin administration alone. We assume that this may be due to a considerably high variability in tumor lesion volumes, rather small number of lesions and relatively short follow-up. Earlier studies demonstrated that the effect of electrochemotherapy depends on the volume of tumor lesions. Smaller lesions responded much better to treatment. These studies on electrochemotherapy reported that, of the lesions that responded to treatment, a high percentage had a volume smaller than 100 mm^3 [4–6,10]. As the lesions in our patients were larger than 7 mm, i.e. larger than the spacing between two electrodes, we obtained a satisfactory electroporation of the lesion by repositioning the electrodes so that the whole surface of the lesion was included. However, it is not yet definitely certain whether the whole lesion is electroporated by this procedure because, upon progression, we noticed that some of them were growing at margins and in depth, i.e. into the skin or s.c. tissue. Our study also proved that smaller lesions responded better to treatment. The mean volume of the lesions that acquired CR to electrochemotherapy was 72 mm^3 and of the lesions that responded only partially was 192 mm^3. This is an indication that bigger tumors were not adequately electroporated, due to inadequate electric field distribution, particularly in deeper layers of the tumors. This issue has already been addressed by using needle electrodes that would be more suitable for electroporation for bigger and deeper seeded tumors [5].

In our study, the lesions were not treated in repeated electrochemotherapeutic sessions. In earlier clinical studies, the lesions in which PR was acquired were further treated with several successive sessions of electrochemotherapy; in these lesions CR was obtained that lasted several months [10,14]. The authors report that, with repeated sessions of electrochemotherapy, they obtained CR even in lesions larger than 200 or 800 mm^3. We did not manage to repeat electrochemotherapy because this would require frequent and regular electrochemotherapeutic sessions and follow-up visits that would additionally exhaust our patients in poor physical condition.

Another challenging question in our study was whether tumors with earlier treatment with cisplatin developed resistance against it and therefore became resistant to additional treatment with cisplatin. It is a general rule that systemic chemotherapy is never repeated by applying the same chemotherapeutic drug, except when the drug proved to be extremely efficient in earlier treatment and if the disease-free interval from the first treatment was reasonably long. In our series of patients, two patients underwent systemic treatment with cisplatin before local treatment. In the first, one lesion that was treated by electrochemotherapy acquired a CR in 2 weeks and one lesion treated by i.t. administration of cisplatin acquired a PR in 2 weeks, too. In the second patient, one lesion that was treated by electrochemotherapy acquired a PR in 2 weeks and lasted for 16 weeks. Based on these results, we may conclude that patients having undergone earlier systemic treatment with cisplatin did not develop resistance to this drug when they were treated with it locally by electrochemotherapy. In the above two patients, all lesions responded to the treatment by electrochemotherapy with cisplatin.

Our results demonstrate that electrochemotherapy with i.t. administration of cisplatin is effective in local control of s.c. tumor lesions of breast cancer. Considering the results of previous studies performed on electrochemotherapy with bleomycin that also included breast cancer patients, electrochemotherapy with cisplatin seems to be less effective. In electrochemotherapy with i.v. administration of bleomycin, a CR was obtained in both tumor lesions of breast cancer treated by this modality, whereas in electrochemotherapy with i.t. administration of bleomycin performed on two breast cancer patients with altogether 14 lesions, CR was obtained in 58% of lesions and PR in 42% of lesions [5,12]. However, both studies on electrochemotherapy with bleomycin, as well as ours, were performed on a small number of tumor lesions; therefore, we cannot make a firm and reliable conclusion which of the two therapies is more effective. To make a final evaluation, one would need to carry out a comparative study on the efficiency electrochemotherapy with i.t. administration of bleomycin and on the efficiency electrochemotherapy with i.t. administration of cisplatin.

With regard to the results of clinical studies on electrochemotherapy performed on other cancer patients, the efficiency of electrochemotherapy with cisplatin seems comparable to the efficiency of electrochemotherapy with bleomycin [4–14]. The results of our study on

cutaneous tumor lesions of breast cancer demonstrate that electrochemotherapy with i.t. administration of cisplatin is as effective in the treatment of this carcinoma as in others. However, in the treatment of cutaneous tumor lesions of malignant melanoma patients, who were so far most often included in the studies on electrochemotherapy, a higher rate of CRs to treatment by i.t. administration of bleomycin or of cisplatin was obtained than in our study on cutaneous lesions of breast cancer. Moreover, it should not be disregarded that the number of the lesions treated in our study was too small and the observation times too short to allow us to conclude that electrochemotherapy of breast cancer cutaneous lesions with i.t. administration of cisplatin is less effective than the same therapy in the treatment of malignant melanoma lesions.

Electrochemotherapy with cisplatin was well tolerated by all female patients and the only male patient in our study. During the study, only local and early side-effects were observed, e.g. muscular contractions in the tumor lesion area during the application of electric pulses, erythema and crust developed at the treatment site to which electric pulses were delivered, and two patients complained of itching, which died away in 4–7 days. Late side-effects were minimal scarring and depigmentation of the skin in the sites of the lesions treated with electrochemotherapy. Immediate or late systemic side-effects were not observed.

Conclusion

The results of our study clearly indicate that electrochemotherapy with i.t. administration of cisplatin is effective in the local control of cutaneous and s.c. tumor lesions of breast cancer. Treatment by electrochemotherapy was more effective than treatment by i.t. cisplatin application alone. Electrochemotherapy resulted in CR that could not be obtained by i.t. cisplatin administration alone. Treatment responses to electrochemotherapy were of longer duration than the responses to treatment by i.t. cisplatin administration alone. The advantages of electrochemotherapy are: easily reproducible method, short treatment time, minimal toxicity and application possible in an outpatient department. However, further studies are needed to ambiguously demonstrate the treatment efficiency of electrochemotherapy of cutaneous tumor lesions of breast cancer. They should include a larger number of patients with a higher number of lesions and longer observation periods.

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