Electrochemotherapy for primary skin cancer and skin metastasis related to other malignancies

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Electrochemotherapy is an effective local tumor ablation modality in the treatment of solid cancers. Its use combines the administration of nonpermeable or poorly permeable highly intrinsic cytotoxic drugs with the application of short and intense electric pulses to the tumors to facilitate the drug delivery into the cancer cells. After several preclinical and clinical studies using different and nonhomogenous protocols, the results of the multicenter European Standard Operating Procedure of Electrochemotherapy (ESOPE) project provided clinical procedures for a standardized, efficient, and safe electric pulse and drug administration protocol for the local treatment of any type of skin tumor nodules. Additional studies using the the multicenter European Standard Operating Procedure of Electrochemotherapy standard operating procedures confirmed the overall clinical results obtained. Currently, the tumors most frequently treated with ECT are melanoma and breast cancer metastasis, but also head and neck cancer, primary tumors of the skin, and Kaposi sarcoma. This review is intended as an update on the therapy and as an indication of possible future developments. *Anti-Cancer Drugs* 22:711–718 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Electrochemotherapy refers to the combination of electroporation and the administration of low doses of anticancer drugs for local treatment of solid neoplasms. Cell membrane electroporation is defined as a transient permeabilization of the cell membrane, induced by the application of short and intense electric pulses that creates direct access to the cell cytosol. The first clinical studies on electrochemotherapy date back to the early 1990s [1] and were reported to be effective in local disease control on tumor nodules of different histological origin. Its use is at present standardized to skin and subcutaneous localizations.

Treatment of skin metastases of different origin, be it melanoma, visceral tumors, or other skin cancers, almost exclusively pursues palliative goals, with the primary choice of surgical excision if technically feasible. Other treatment options are radiotherapy and systemic therapy [2]. At present, electrochemotherapy constitutes an additional therapeutic tool in selected patients, refractory/relapsed after conventional therapies, which is able to provide relief from cutaneous metastases that hold psychological and physiological strain for the patient, thus improving the patient's quality of life. This study is intended as an update on the therapy and as an indication of possible future developments.

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In-vitro and in-vivo studies

Application of an external electric field generates a change in the cell transmembrane potentials. At the cell membrane level, it has been established that applying electric fields above the threshold value of the transmembrane potential (approximately 1.5 V) [3] results in changes in the membrane structure that render the membrane permeable to otherwise nonpermeant molecules [4], a phenomenon termed electroporation or electropermeabilization. One accepted theory explaining cell electroporation is based on the finding that the application of electric fields generates a large number of transient electropores with a half-life in the order of 1 μs, and a reduced number of more stable longer-lived electropores. This phenomenon is considered to be responsible for the passage of molecules across the membrane. Therefore, after exposure to appropriate electric pulses, small hydrophilic molecules are able to cross the plasma membrane and enter the cytosol, by simply diffusing through the cell membrane. Of note, cell membrane permeability is not indefinite, but lasts several minutes after exposure to the electric pulses [5].

Electroporation of cells results in enhanced drug diffusion through the cell membrane. On account of the changes that occur to the cell membrane, suitable drug candidates for the combined use with electric pulses are the hydrophilic drugs, or those lacking transport systems into the membrane. During early in-vitro preclinical experiences, several chemotherapeutic drugs have been tested

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for potential application in combination with electroporation, including bleomycin, daunorubicin, doxorubicin, etoposide, paclitaxel, actinomycin D, adriamycin, mitomycin C, 5-fluorouracil, vinblastine, vincristine, gemcitabine, cyclophosphamide, carboplatin, and cisplatin [6–9]. It was observed that enhanced diffusion through the plasma membrane occurred after electric pulse delivery, resulting in an increase in the antitumor effect of some of these drugs ranging anywhere from 1.1-fold to 80-fold for cisplatin and several thousand folds for bleomycin [10]. On the basis of these findings, in-vivo preclinical and clinical researches on the efficacy of electrochemotherapy focused on cisplatin, or bleomycin, in combination with electroporation.

It was determined by in-vitro studies that transport of bleomycin across a nonpermeabilized plasma membrane is limited by the low number of carrier proteins exposed at the cell surface, and by the withdrawal of these proteins from the membrane due to endocytosis [11]; this mechanism curbs the uptake of bleomycin in nonelectroporated cells. To facilitate the diffusion of bleomycin through the cell membrane, local electropermeabilization of cells can be used; the physical changes induced in the cell membrane enable diffusion of bleomycin into the cell, direct access to the cytosol, and transport to the nucleus, in which it exerts its cytotoxic activity [12–14].

Moreover, the mechanism of action of bleomycin is not modified by the application of electric pulses. It has been shown that the induced cell death is mediated by the generation of DNA breaks effected by bleomycin, the same mechanism that results in cell death when diffusion of bleomycin occurs through the nonpermeabilized membrane. In fact, it has been observed that the activity of bleomycin on isolated DNA is not affected by exposure to electric pulses [14–16]. Cisplatin transport through the nonpermeabilized plasma membrane is also hampered. Electroporation of the plasma membrane enables increased flux and accumulation of the drug in cells, which results in an increase of cisplatin cytotoxicity by up to 80-fold [17]. This increase in cisplatin uptake and DNA adducts generation is significant; however, it is still lower than in the case of bleomycin [10].

On basis of these studies, bleomycin and cisplatin were found to be optimal candidates for use in the context of a local combination therapy based on tissue electroporation and low drug administration. Initial laboratory experiments showed that the optimal parameters for cell membrane permeabilization are eight consecutive square-wave electric pulses of 100 μs duration, delivered at a repetition frequency of 1 Hz [9]. In addition, electroporation achieved by delivering pulses at a repetition frequency of 5000 Hz allows for a shortening of the treatment duration with no decrease in treatment efficacy [18]. However, a recent in-vivo study suggests that if drug doses are suboptimal, a repetition frequency of 1 Hz may be more effective than a repetition frequency of 5000 Hz [19].

In-vivo studies defined the local electric field threshold value for cell electroporation in various tissues. Using the optimal parameters of eight square-wave electric pulses of 100 μs (i.e. electrochemotherapy conditions), the threshold values for tumors, skeletal muscle, and the liver were determined to be between 300 and 500 V/cm, 450 and 360 ± 20 V/cm, respectively [4,20,21]. Effectiveness of electrochemotherapy thus depends on drug availability in the tumor and treatment of the whole tumor volume by appropriate electrical parameters to ensure complete eradication of malignant cells [22].

Extensive in-vivo studies have been conducted evaluating the antitumor effectiveness of electrochemotherapy using bleomycin, or cisplatin, on different animal tumor types, either transplantable or spontaneous. In these studies, solid subcutaneous tumors in the muscle, liver, or brain, either sarcomas, carcinomas, melanoma, or neuroblastoma, were used to show the antitumor effectiveness of electrochemotherapy. Different administration routes, dosages, and timing of drug administration, as well as the electrical parameters used by the electroporation device were evaluated during these studies. Overall, these studies showed a high complete response (CR) rate (up to 75%) for tumors treated with electrochemotherapy. Particularly, high antitumor effectiveness was shown for fibrosarcomas, melanoma, and carcinomas in mice, rats, and rabbits. In addition, favorable results are routinely obtained in veterinary medicine when used on cats, dogs, and horses [10,23–36]. During electrochemotherapy procedures, electric pulse delivery is associated with contraction of the muscles underlying the treated area [37]. To this day, muscle contraction constitutes the most often encountered side effect of electrochemotherapy. It has also been shown that application of electric pulses to the cells does not significantly change the expression profile of major tumor suppressor genes or oncogenes of the cell cycle. Moreover, electroporation does not change the expression of genes involved in the stability of DNA and does not increase the metastatic potential of cells that survive with electrochemotherapy [38,39].

Early clinical studies

The following reported clinical studies evaluated the use of electrochemotherapy in the treatment of various types of primary skin cancers, cancers of the head and neck, and skin metastases of different origin. These studies were conducted with varying treatment protocols, electrodes, and electric pulse generators and provide evidence of the antitumor effectiveness and safety of electrochemotherapy.

The first study on the use of electrochemotherapy in the treatment of cancer patients was by Mir *et al.* [1] in 1991, followed by the study by Belehradek *et al.* [40] in 1993. This phase I/II study showed antitumor effectiveness of

bleomycin given intravenously followed by electroporation of tumor volume. The clinical study included eight cancer patients with 40 head-and-neck squamous cell carcinoma nodules. Objective responses (ORs) were obtained in 72% of nodules; CR was obtained in 57% of the treated nodules. In contrast, the tumor nodules that were treated with bleomycin alone (without electroporation) did not respond to the treatment. No major side effects were reported. This first clinical study showed the feasibility and preliminary effectiveness of electrochemotherapy using intravenously administered bleomycin.

The use of bleomycin administered intralesionally with electroporation was introduced in 1996 [41]. The study involved five patients with 23 melanoma metastases. OR rate was observed in 95% of the treated nodules, with 78% CR.

A first clinical study of electrochemotherapy with intratumoral injection of cisplatin on cutaneous tumor nodules of patients with malignant melanoma, squamous cell carcinoma, and basal cell carcinoma, was performed by Sersa *et al.* [42] in 1998. In four patients, CR of all 19 electrochemotherapy-treated nodules was obtained. A phase II study was then conducted. In 10 patients, 133 tumor nodules were treated: 82 tumor nodules were treated with electrochemotherapy using intratumoral cisplatin, 27 were treated with cisplatin, two with electric pulses alone, and 22 were not treated. At 4 weeks after therapy, OR was observed in 78% of nodules, 68% achieved CR, and 10% had a partial response (PR). At 124 weeks, local tumor control rates were 77% for the electrochemotherapy group and 19% for the cisplatin-alone group [43]. Early clinical experiences show that electroporation, in combination with bleomycin or cisplatin, is an effective treatment of cutaneous tumor nodules.

Recently, Sersa [44] provided a comprehensive analysis of clinical studies conducted with electrochemotherapy using bleomycin and cisplatin, up through 2006. A summary of the data from these studies is provided below, divided into melanoma (Table 1) and nonmelanoma (Table 2) tumors. Histology of the nonmelanoma electrochemotherapy-treated tumors included head and neck squamous cell carcinoma, basal cell carcinoma, breast adenocarcinoma, salivary gland carcinoma, hypernephroma, Kaposi's sarcoma, bladder transitional cell carcinoma, head and neck adenocarcinoma, chondrosarcoma, and adenocarcinoma tubae. Overall early clinical trials report electrochemotherapy treatment results of 247 patients, presenting with 1009 nodules, with a CR rate ranging from 11%, results obtained in a single clinical trial investigating the efficacy of electrochemotherapy with cisplatin administered intravenously, to 77% and an OR rate ranging from 48 to 90%.

Table 1 Electrochemotherapy clinical trials on melanoma tumours conducted before 2006

Drug and administration route	Number of patients included	Number of nodules treated	CR rate (%)	OR rate (%)
Bleomycin (i.v.)	16	119	54 (45)	105 (88)
Bleomycin (i.t.)	42	189	146 (77)	170 (90)
Cisplatin (i.v.)	9	27	3 (11)	13 (48)
Cisplatin (i.t.)	27	307	227 (74)	256 (83)
Total	94	642	430 (67)	544 (85)

Adapted with permission from [44].
CR, complete response; i.t., intratumoral; i.v., intravenous; OR, objective response.

Table 2 Electrochemotherapy clinical trials on nonmelanoma tumours conducted before 2006

Drug and administration route	Number of patients included	Number of nodules treated	CR rate (%)	OR rate (%)
Bleomycin (i.v.)	27	150	80 (53)	105 (70)
Bleomycin (i.t.)	117	197	123 (63)	165 (84)
Cisplatin (i.t.)	9	20	10 (50)	20 (100)
Total	153	367	213 (58)	290 (79)

Adapted with permission from [44].
CR, complete response; i.t., intratumoural; i.v., intravenous; OR, objective response.

These studies, conducted using electrochemothrapy with bleomycin or cisplatin administered intravenously or intratumorally, showed consistent and clear evidence of clinical efficacy and safety profile in the treatment of cutaneous neoplasms of different histology.

A prospective, multicenter, international study, the European Standard Operating Procedures of Elctrochemotherapy (ESOPE) study, was launched in 2003 to evaluate, under a unified treatment protocol, the efficacy and safety of electrochemotherapy with bleomycin or cisplatin on cutaneous and subcutaneous tumor nodules of patients with melanoma and other malignancies. The endpoints, relating to local control and palliation of cutaneous neoplasms, of the ESOPE study were to (i) determine the OR rate and CR rate of electrochemotherapy according to the World Health Organisation (WHO) criteria; (ii) investigate the efficacy of two different drugs used in electrochemotherapy and the influence of the route administration; (iii) determine the treatment response according to the tumor type, size, location, type of electrodes, and electrical parameters, and the cancer center where the treatment was performed; and (iv) evaluate the toxicity and document the safety of the treatment. The ESOPE study (QLK3-2002-02003) was funded by the European Commission's Fifth Framework Programme of Research (FP5) [45].

Within the study, the treatment protocol was unified through the definition of electrochemotherapy standard operating procedures [46]: electric pulses could be delivered by one of the three different types of electrodes; for each electrode pulse, parameters were selected to ensure homogeneous electroporation of tumor cells in the treated area. Drug administration could be performed intravenously for bleomycin, dosed accordingly to the

patient body surface area, or intratumorally for bleomycin and cisplatin, dosed accordingly to the tumor volume.

Treatment response after electrochemotherapy according to the type of tumor, drug used, route of administration, and type of electrode was analyzed [45]. An OR rate of 85% (73.7% CR rate) was achieved in 171 electrochemotherapy-treated tumor nodules on 41 patients. Cutaneous and subcutaneous nodules of melanoma were treated predominantly, followed by breast cancer, colon cancer, squamous cell carcinoma of the skin, squamous cell carcinoma of the cervix, Kaposi's sarcoma, and leiomyosarcoma cutaneous and subcutaneous tumor nodules in decreasing frequency. Response rate was similar when using electrochemotherapy with bleomycin (intravenous), bleomycin (intratumoral), or cisplatin (intratumoral) (Fig. 1). At 150 days after treatment, the local tumor control rate was 88% with bleomycin (intravenous), 73% with bleomycin (intratumoral), and 75% with cisplatin (intratumoral).

A separate analysis evaluating the treatment of metastatic melanoma and nodules arising from different types of cancer shows an OR rate comparable to the overall study results (Fig. 2).

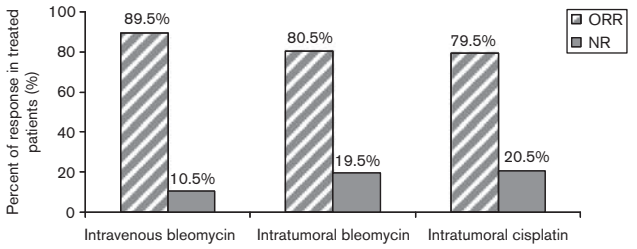
Overall, the results of the ESOPE study show that electrochemotherapy is effective in achieving local control and palliation of metastatic neoplasms located at cutaneous and subcutaneous tissue levels regardless of their histological origin. Effectiveness of electrochemotherapy when using systemically administered bleomycin is comparable to electrochemotherapy OR rate obtained with intratumoral drug administration (cisplatin or bleomicyn) [45].

Subsequent to the ESOPE study, additional studies have been reported using the same standard operating procedures established during the ESOPE study and confirming the overall clinical results obtained [47–49]. Interim results from an international prospective case registry that has been enrolling patients since 2007 and is currently active, the International Network for Sharing Practice in ElectroChemoTherapy database, also support the efficacy of electrochemotherapy in the routine treatment of skin metastases reducing their size and associated symptoms [50]. An Italian muticentric prospective study of electrochemotherapy on patients with cutaneous and subcutaneous metastases, conducted under the auspices of the Italian Melanoma Intergroup and Gruppo Italiano Dermatologia Oncologica groups, is actively enrolling up to 600 patients to evaluate local progression-free disease, patient's quality of life, and local response (personal communication).

When reviewing the existing literature, no reports of serious adverse events or undesirable major toxic effects due to the treatment were found proving the safety of electrochemotherapy [47–50].

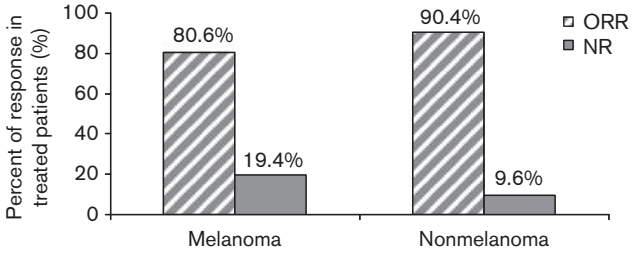
An evaluation of electrochemotherapy-reported applications on cutaneous and subcutaneous metastases leads to the identification of three main clinical areas representing the majority of treatments performed: malignant melanoma, breast cancer recurrences/skin metastasis, and malignancies of the head and neck.

Fig. 1



Objective response rate (ORR) versus no response (NR) rate in nodules treated with bleomycin (intravenous or intratumoral) and cisplatin (intratumoral). Adapted with permission from [45].

Fig. 2



Objective response rate (ORR) versus no response (NR) rate in melanoma and nonmelanoma nodules. Adapted with permission from [45].

Eletcrochemotherapy in the treatment of malignant melanoma

Quaglino *et al.* [47] reported their experience with electrochemotherapy with intravenous bleomycin in patients with metastatic melanoma. In their cohort of 14 stage III relapsed/refractory patients, a series of 233 cutaneous melanoma metastases was included. An OR was obtained in 13 of 14 patients (93%) after the first session, with a CR in seven patients (50%). The analysis conducted showed no differences in response rate between cutaneous and subcutaneous metastases. However, the researchers noted that lesion size was the most predictive parameter for response: a response was obtained in 99% of metastases of size $\leq 1\,cm^2$ and in 83% larger lesions ($P < 0.001$). The difference in response rate was even higher when the CR rate was compared 72% in metastases of size $\leq 1\,cm^2$ versus 28% in lesions measuring $> 1\,cm^2$ ($P < 0.001$). Moreover, treatment repetition allowed an increase in CR rate in lesions showing only PR after the first treatment. CR of treated lesion was

confirmed by histological analysis, and none of the lesions that achieved CR relapsed. Overall, the local tumor control rate was 74.5% at 2 years. Long-term lesion resolution in melanoma patients treated with electrochemotherapy has also been reported when using intralesional cisplatin administration, which also confirms that electrochemotherapy can be repeated several times with equally good antitumor effectiveness [51]. Electrochemotherapy has also been used as a limb-sparing treatment, effectively avoiding amputation, in a patient presenting with bleeding melanoma metastasis [52] and as a cytoreductive treatment before surgical resection and/or adjuvant therapy [53]. Treatment of a primary melanoma of the anal canal and a recurrence of a vulvar melanoma in separate patients, at the same institution allowed local disease control without amputation surgery [54]. In a palliative setting, the advantages of electrochemotherapy are one-time treatment, the low level of side effects, and the option to repeat the treatment to effectively control disease progression to the skin [55].

Campana *et al.* [48] reported the results of electrochemotherapy treatment with bleomycin on 52 patients with a total of 608 cutaneous and subcutaneous metastases, of which 373 were of malignant melanomas. Treatment was well tolerated, especially under general sedation. An OR was obtained in 50 of 52 (96%) patients 1 month after the first application. The researchers concluded that in a palliative setting, electroporation proved to be safe and effective in all tumors treated, and useful in preserving patients' quality of life as assessed through a self-developed questionnaire.

In addition to the treatment of melanoma lesions, early clinical reports, the ESOPE study, and following case series [45,47–49] clearly confirm the clinical efficacy of electrochemotherapy for the treatment of cutaneous and subcutaneous nodules regardless of their histological origin.

Electrochemotherapy has been successfully used in the treatment of skin tumors other than melanoma, such as Kaposi's sarcomas [56–58], metastatic basal cell carcinoma with squamous cell differentiation [59], and Merkel cell carcinoma [60].

Electrochemotherapy in the treatment of breast cancer

Patients presenting with recurrence of breast cancer on the chest wall or skin metastasis have been treated with electrochemotherapy as the first clinical experiences were reported using bleomycin or cisplatin given intravenously or intratumorally (reviewed in ref. [44]). After the publication of the ESOPE study [46], Larkin *et al.* [49] reported the outcomes of their initial experience with electrochemotherapy on 30 patients and 111 skin lesions, of these 17 patients presented with 100 nodules of histologically proven breast cancer. An objective clinical response was obtained in 85% of patients with breast carcinoma. In addition, the researchers noted that repeat treatment may be given in patients for further recurrences of cutaneous metastases. Multiple interval recurrences are often a feature of breast cancer and local disease control achievable using surgery may be challenging or contraindicated due to the size of the area to be resected or if the management of a systemic disease is necessary. For these reasons a treatment option highly effective and with low therapeutic burden for the patients, such as electrochemotherapy, can have an important positive impact on local disease management. PRs and palliation of symptoms may also be of benefit to some patients, not only in arresting tumor progression, but in providing substantial symptomatic relief in patients with larger, painful, bleeding, and discharging lesions. Campana *et al.* [48] observed a similar clinical response in 11 patients (174 nodules) who were treated at Istituto Oncologico Veneto, Padova, Italy.

Electrochemotherapy in the treatment of head and neck cancer

Electrochemotherapy has also found application in the treatment of head and neck cancer. A first study of electrochemotherapy using intralesional bleomycin in 10 patients (8 SCCs, 1 adenocarcinoma, 1 adenoid cystic adenocarcinoma with parotid involvement) reported five CR, three PR, and two NR at a mean follow-up time of 40 weeks [61]. In this series, the results were confirmed by MRI and biopsy. In a multicenter phase II trial, 42 patients with 51 tumor recurrences were treated with electrochemotherapy using intralesional bleomycin. OR ratio was 57% (24% CR, 33% PR); however, an increase in survival from 3 to 6.4 months was observed [62]. Another study enrolled 12 patients with primary T1 and T2 squamous cell cancers of the head and neck, tumors were treated using intralesional bleomycin and resected after 4 weeks of follow-up. Pathological examination found residual disease in only two of 12 specimens with no evidence of recurrence for the duration of the trial [63]. In a report summarizing two open-label, multicenter, single-arm phase II studies of intratumor bleomycin administration and electrochemotherapy, 62 patients with 86 squamous cell carcinoma tumors of the head and neck were enrolled. Twenty-five patients were treated with bleomycin alone. Fifty-four patients (17 initially treated with bleomycin alone) were treated with electrochemotherapy and bleomycin. In the bleomycin-alone group, one tumor showed a PR and 36 tumors showed no response to treatment. In the bleomycin with electrochemotherapy groups, 17 tumors showed CR, 22 tumors showed a PR and 30 failed to achieve more than a 50% reduction in tumor size (no response) with 57% overall OR rate. Electrochemotherapy with bleomycin had a significantly (t-test; $P < 0.001$) greater number of patients showing a PR or CR to the therapy when compared with bleomycin alone [64].

More recently, Gargiulo *et al.* [65] reported their results of electrochemotherapy of the head and neck using intravenous bleomycin. A total of 15 patients were treated (9 squamocellular carcinoma, 5 basocellular carcinoma, and 1 Bowen's disease) according to ESOPE standardized procedures [46]. According to the WHO criteria, CR was achieved in 12 of 15 (80%) tumors treated whereas PR was obtained in the remaining three tumors (20%). Given their results, the researchers suggest a neoadjuvant role of electrochemotherapy for those cases in which surgical procedures alone would be too invasive to achieve oncological radicality. The researchers also foresee a role for electrochemotherapy as a first-line treatment of head and neck cancers [65].

Future perspectives of electrochemotherapy

Recent discoveries suggest that in addition to the direct cytotoxic effect of electrochemotherapy on tumor cells, there may also be an indirect effect on the tumor, as electric pulses have a blood-flow-modifying action and a vascular-disrupting effect. This is shown by a rapid shutdown of blood flow to tumors, leading to reduced tumor oxygenation, increased tumor hypoxia, and extensive tumor necrosis [66]. These effects may help explain the immediate symptom palliation commonly reported by investigators in the treatment of bleeding or ulcerating metastasis as well as offer the basis to investigate possible combination therapy involving electrochemotherapy and antiangiogenic factors.

Moreover, because of the mechanisms of its action, electrochemotherapy selectively kills tumor cells without denaturating the proteins. It has been proposed that electrochemotherapy might allow tumor antigen shedding and local inflammation, thus attracting immune antigen-presenting cells. A crucial role for the immune system has been shown in preclinical studies, when electrochemotherapy efficacy was compared using the same tumor cells inoculated into immunocompetent or immunodeficient mice, in which complete remissions were found only in the immunocompetent mice [67,68]. Low amounts of interleukin-2 (IL-2) were then added locally at the treated site on the days after electrochemotherapy and the number of cures increased in the immunocompetent mice [69]. Furthermore, the combined treatment of electrochemotherapy and intratumoral injection of IL-2-secreting cells resulted in the potentiation of antimetastatic effect [27,70,71]. Similar increases in antitumor effectiveness were observed in immunocompetent mice treated with electrochemotherapy in combination with TNF-α [72]. A clinical study on electrochemotherapy and low-dose IL-2 has shown durable clinical responses [73] as well as responses in circulating lymphocytes, in a subset of patients. Finally, recent preclinical work has shown first the stimulation and recruitment of dendritic cells by electrochemotherapy on the site of tumor damage and the generation of systemic antitumor effects by the combination of electrochemotherapy and the immune adjuvant TLR ligand (CpG ODN) molecules, through the activation of T cells [74]. The combination of electrochemotherapy capable of inducing cell death, while exposing intact tumor antigens, with immunostimulants to elicit an effective immune response with systemic anticancer effect targeting metastatic cells, could result in an effective self-driven immunotherapy for systemic tumor control, of indications still difficult to treat. Moreover, this combined therapy would have the advantage of not being so invasive and devastating such as the chemotherapies that are in use now.

Currently, the main limitation faced by electrochemotherapy users is represented by the maximum tumor thickness and tissue depth of 3 cm of treatable tumors [46,48] and the current use limited to nodules located at the cutaneous or subcutaneous level. However, the first reports of feasibility, safety, and technological advances needed to allow treatment of visceral and deep-seated tumors with electrochemotherapy, are emerging [75], as well as the intraoperative application of current technology and operating procedures for the treatment of disseminated visceral metastasis [76].

Conclusion

Clinical application of electrochemotherapy to the treatment of primary skin cancers and skin metastases related to other malignancies has been consistently expanding in the past two decades [1,65]. Preclinical developments before the use of electrochemotherapy first in human patients, and subsequent research, helped define its mechanism of action, the most effective treatment parameters, both electrical and pharmacological, and the most suitable operating procedures [3–39] for safe and reproducible treatments. Electrochemotherapy has been repeatedly and independently shown to be highly effective in providing local tumor control and palliation of symptomatic lesions located in cutaneous or subcutaneous tissues regardless of their histological origin, while maintaining a very low toxicity profile and high patient acceptance [40–45,47–65].

More recent clinical evidence [47,48] supports earlier electrochemotherapy use to treat smaller lesions, to improve efficacy and eradicate target nodules in one treatment session thereby reducing therapeutic burden to the patient. Thanks to the ongoing long-term prospective case registries [50], the impact of electrochemotherapy on disease progression is being investigated.

Although the treatment of smaller lesions results in higher CR rates, electrochemotherapy has also proven to be effective in palliation of symptomatic lesions and as a neoadjuvant treatment to allow for less invasive surgical approaches [65]. The low toxicity of the treatment and lack of side effects make it an ideal candidate for patients

with poor performance status, or with important comorbidities, which may render them unsuitable for surgery.

The efficacy of electrochemotherapy on local control of superficial lesions has been well established. In addition, early clinical evidence supports investigation of electrochemotherapy application beyond the skin to visceral metastases. In the longer term, the association of electrochemotherapy with appropriate immunomodulant stimuli holds promise for the translation of local disease control to a systemic response mediated by the patient's immune system.

Acknowledgement

Conflicts of interest

None declared.

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