available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

The state-of-the-art of electrochemotherapy before the ESOPE study; advantages and clinical uses

*Gregor Sersa**

Institute of Oncology Ljubljana, Zaloska 2, SI-1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 19 June 2006
Received in revised form
1 July 2006
Accepted 4 August 2006

Keywords:
Electrochemotherapy
Bleomycin
Cisplatin
Electroporation

ABSTRACT

Electrochemotherapy provides effective local control of cutaneous and subcutaneous tumour nodules of different malignancies. High objective response rate of ~80% treated nodules was reported in the majority of clinical studies, with 30–100% long lasting complete responses. This high level of local tumour control was obtained with either systemic drug injection (bleomycin) or local drug injection (cisplatin or bleomycin) with subsequent application of electric pulses to the tumour nodules. The treatment is mostly used for palliation and has in case of in transit metastases of melanoma significant clinical benefit and impact on the quality of life. Furthermore, other clinical uses of electrochemotherapy are: neoadjuvant treatment in form of cytoreductive treatment before conventional treatments, organ and function sparing treatment and treatment of choice of painful and haemorrhagic nodules. Intraoperative treatment of tumours and development of endoluminal electrodes will bring new indications for electrochemotherapy.

1. Introduction

The first clinical study on electrochemotherapy was published in 1991, reporting good treatment effectiveness of electrochemotherapy on cutaneous tumour nodules of head and neck tumours.[1] The results of that study, which was preformed by the group from the Institute Gustave Roussy, Villejuif, France have stimulated other groups to initiate their own clinical studies. The first clinical centres which performed electrochemotherapy in addition to Institute Gustave Roussy, were our group at the Institute of Oncology Ljubljana, Slovenia, the group at the University of South Florida in Tampa, USA, and the group at Institute of Pharmacology and Structural Biology and Institute Claudius Regaud in Toulouse, France.[2–5] Recently, also new centres reported clinical experience on electrochemotherapy, e.g. Rush Presbyterian-St. Luke's Medical Center, Chicago, USA, Yamagata University School of Medicine, Yamagata, Japan, Herlev Hospital, Herlev, Denmark, Instituto Mexicano del Seguro Social, Mexico City, Mexico, General Hospital of Vienna, Austria, Shinshu University School of Medicine, Matsumoto, Japan, University of Sidney, Sydney, Australia, Naval Medical Center Portsmouth, Portsmouth, USA.[6–13]

In all clinical studies reported so far before the European Standard Operating Procedures of Electrochemotherapy (ESOPE) study 247 patients were included; 202 patients with 655 tumour nodules were treated by electrochemotherapy with bleomycin and 45 patients with 354 tumour nodules were treated by electrochemotherapy with cisplatin. The majority of patients included in the studies were patients with melanoma metastases, followed by patients with metastases of skin, head and neck, mammary, ovarian cancer, Kaposi's sarcoma and chondrosarcoma. The results of the studies can be summarised as having good antitumour

* Tel./fax: +386 5879 434.
E-mail address: gsersa@onko-i.si.
1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2006.08.007

effectiveness using either bleomycin or cisplatin, resulting in ~80% objective responses of the treated tumour nodules.

2. Overview of clinical trials

There are several papers dealing with overview of the clinical data on electrochemotherapy where detailed analyses of the results were presented.[14–16] In addition to that, extensive list of references on clinical studies of electrochemotherapy reporting its effectiveness on different types of tumours is provided in the reference list of this paper[1–13,16–32] (Tables 1 and 2). In the present report, I would like to point out some clinical studies that were milestones in introduction of electrochemotherapy in treatment of tumours.

The first report on the use of electrochemotherapy in treatment of cancer patients was by Mir et al. from Institute Gustave Roussy, Villejuif, France in 1991 and 1993.[1,2] This phase I/II study was launched after preclinical studies demonstrating good antitumour effectiveness of bleomycin given intravenously and subsequent electroporation of the tumours, which is discussed in this issue in the article of L.M. Mir. In the clinical study 8 cancer patients with 40 head and neck squamous carcinoma nodules were treated. Objective responses were obtained in 72% and among these complete responses were obtained in 57% of the treated nodules. The tumour nodules that were treated with bleomycin only did not respond to the treatment. No side effects were reported, and even repetitive treatment proved to be successful. This first clinical study demonstrated feasibility and also effectiveness of electrochemotherapy, as well as it indicated that electrochemotherapy may be effective also on tumours of different histological origin, due to the theoretical basis of electroporation principle for drug delivery. This was proved by other groups from Toulouse, France, Tampa, USA, and Ljubljana, Slovenia, which launched their own clinical trials on electrochemotherapy with bleomycin given intravenously on different tumour types, namely melanoma, basal cell carcinoma, and adenocarcinoma.[3,5,18]

New approach in electrochemotherapy, the use of bleomycin given intratumourally was introduced in 1996 by Heller's group from Tampa, USA.[17] That study involved 5 patients with 23 melanoma metastases that were treated by electrochemotherapy with bleomycin given intratumourally. Very good antitumour effectiveness was observed. Objective response rate was 95%, with 78% of complete responses. Altogether, these first studies using electrochemotherapy with bleomycin given either intravenously or intratumourally demonstrated that this treatment approach is effective on cutaneous tumour nodules of different histology with good local tumour control.

Results of all clinical trials performed in five cancer centres that have been involved in electrochemotherapy, were summarised in 1998 by Mir et al.[21] The results were gathered from Institute Gustave Roussy, Villejuif, France, University of South Forida, Tampa, USA, Institute of Oncology, Ljubljana,

Table 1 – Clinical trials with electrochemotherapy on melanoma tumours

Reference	# of patients	# of nodules	Response				
			PD (%)	NC (%)	PR (%)	CR (%)	OR (%)
Bleomycin i.v.							
Rudolf[3]	2	24	1 (4)	1 (4)	0	22 (92)	22 (92)
Heller[18]	3	10	0	5 (50)	2 (20)	3 (30)	5 (50)
Mir[21]	7	30	1 (3)	2 (7)	3 (10)	24 (80)	27 (90)
Rols[5]	4	55	0	4 (7)	46 (84)	5 (9)	51 (93)
Sub-total	16	119	2 (2)	12 (10)	51 (43)	54 (45)	105 (88)
Bleomycin i.t.							
Glass[17]	5	23	0	1 (4)	4 (17)	18 (78)	22 (96)
Heller[22]	12	84	0	1 (1)	8 (10)	75 (89)	83 (99)
Gehl[8]	1	9	0	0	0	9 (100)	9 (100)
Rodriguez[9]	2	13	0	2 (15)	8 (62)	3 (23)	11 (85)
Byrne[12]	21	52	5 (10)	10 (19)	4 (8)	33 (63)	37 (71)
Kubota[7]	1	8	0	0	0	8 (100)	8 (100)
Sub-total	42	189	5 (3)	14 (7)	24 (13)	146 (77)	170 (90)
Cisplatin i.v.							
Sersa[27]	9	27	3 (11)	11 (41)	10 (37)	3 (11)	13 (48)
Cisplatin i.t.							
Sersa[23]	2	13	0	0	0	13 (100)	13 (100)
Sersa[28]	10	82	5 (6)	6 (7)	5 (6)	66 (80)	71 (87)
Sersa[16]	14	211	16 (8)	24 (11)	23 (11)	148 (70)	171 (81)
Snoj[30]	1	1	0	0	1 (100)	0	1 (100)
Sub-total	27	307	21 (7)	30 (10)	29 (9)	227 (74)	256 (83)
Total	94	642	31 (5)	67 (10)	114 (18)	430 (67)	544 (85)

Table 2 – Clinical trials with electrochemotherapy on non-melanoma tumours

Reference	Histology	# of patients	# of nodules	Response				
				PD (%)	NC (%)	PR (%)	CR (%)	OR (%)
Bleomycin i.v.								
Belehradek[2]	HN SCC[a]	8	37	0	8 (22)	6 (16)	23 (62)	29 (78)
Mir[21]	HN SCC	13	77	21 (27)	8 (10)	15 (19)	33 (43)	48 (62)
Glass[4]	Basal cell carcinoma	2	6	0	0	4 (67)	2 (33)	6 (100)
Heller[18]	Breast adeno ca.	1	2	0	0	0	2 (100)	2 (100)
Domenge[19]	Breast adeno ca.	1	7	7 (100)	0	0	0	0
Domenge[19]	Salivary gland adeno ca.	1	20	0	0	0	20 (100)	20 (100)
Sersa[26]	Hypernephroma	1	1	0	1 (100)	0	0	0
Sub-total		27	150	28 (19)	17 (11)	25 (17)	80 (53)	105 (70)
Bleomycin i.t.								
Heller[22]	SCC	1	1	0	0	1 (100)	0	1 (100)
Panje[6]	HN SCC	8	8	0	2 (25)	2 (25)	4 (50)	6 (75)
Alegretti[32]	HN SCC	4	4	0	0	2 (50)	2 (50)	4 (75)
Rodriguez[9]	HN SCC	2	2	0	0	2 (100)	0	2 (100)
Burian[10]	HN SCC	12	12	0	0	2 (17)	10 (83)	12 (100)
Bloom[13]	HN SCC	54	69	0	30 (43)	22 (32)	17 (25)	39 (57)
Glass[20]	Basal cell ca.	20	54	0	0	1 (2)	53 (98)	54 (100)
Rodriguez[9]	Basal cell ca.	9	9	0	0	2 (22)	7 (78)	9 (100)
Heller[22]	Kaposi's sarcoma	1	4	0	0	0	4 (100)	4 (100)
Kubota[7]	Bladder transitional cell ca.	1	17	0	0	0	17 (100)	17 (100)
Panje[6]	HN adeno ca.	2	2	0	0	1 (50)	1 (50)	2 (100)
Rodriguez[9]	Breast ca.	2	14	0	0	6 (43)	8 (57)	14 (100)
Shimizu[11]	Chondrosarcoma	1	1	0	0	1 (100)	0	1 (100)
Sub-total		117	197	0 (0)	32 (16)	42 (21)	123 (63)	165 (84)
Cisplatin i.t.								
Sersa[23]	SCC	1	2	0	0	0	2 (100)	2 (100)
Sersa[23]	Basal cell ca.	1	4	0	0	0	4 (100)	4 (100)
Sersa[23]	Adeno ca. tubae	1	2	0	0	2 (100)	0	2 (100)
Rebersek[29]	Breast ca.	6	12	0	0	8 (67)	4 (33)	12 (100)
Sub-total		9	20	0 (0)	0 (0)	10 (50)	10 (50)	20 (100)
Total		153	367	28 (8)	49 (13)	77 (21)	213 (58)	290 (79)

a Head and neck Squamous Cell Carcinoma.

Slovenia, Centre Claudius-Régaud, Toulouse, France and Institut Jean-Godinot, Reims, France. Clinical experience on electrochemotherapy with bleomycin given either intravenously or intratumourally on 291 cutaneous or subcutaneous tumour nodules in 50 cancer patients was reported. Electrochemotherapy was performed on tumour nodules originating from basal cell carcinoma (32), melanoma (142), adenocarcinoma (30), and head and neck squamous cell carcinoma (87). Objective responses were obtained in 233 (85%) of the 273 evaluable tumour nodules that were treated with electrochemotherapy, from these 154 (56%) tumour nodules were in complete response (Tables 1 and 2). This study clearly demonstrated that electrochemotherapy with bleomycin is effective in treatment of tumour nodules with different histology, and that the results of the treatment were comparable between the five cancer centres, in spite of small differences in treatment protocols that they used.

The next milestone was the introduction of cisplatin, a widely used chemotherapeutic drug, into electrochemotherapy protocol. The first reports on electrochemotherapy with cisplatin were by Sersa et al. from Institute of Oncology Ljubljana, Slovenia in 1998.[23,28] In separate publications the results on antitumour effectiveness of electrochemotherapy with cisplatin given intravenously or intratumourally on melanoma, basal cell, squamous cell and adeno carcinoma tumour nodules were presented. In the first study, application of electric pulses was performed on accessible melanoma tumour nodules in patients that were receiving standard intravenous cisplatin-based chemotherapy regimen. The antitumour effectiveness of electrochemotherapy, i.e. application of electric pulses to tumour nodules together with cisplatin-based therapy was compared to the antitumour effectiveness of cisplatin-based therapy given intravenously alone.[27] In 9 malignant melanoma patients, electrochemotherapy resulted in 48% objective responses of 27 treated nodules, whereas in 18 tumour nodules treated with cisplatin-based therapy 22% objective response rate of the tumour nodules was obtained. Furthermore, the median time to progression was longer in electrochemotherapy treated nodules (21 weeks) than in the cisplatin-based therapy treated nodules (4 weeks). It has to be emphasised that the treated tumour nodules in that study were much bigger than

those treated in studies using bleomycin; therefore, it could be expected that the response rate was lower. However, no further attempt to introduce electrochemotherapy using cisplatin given intravenously was made, based on the good results obtained using electrochemotherapy with bleomycin, given intravenously and electrochemotherapy with cisplatin, given intratumourally.

The second study presented the results on electrochemotherapy with cisplatin given intratumourally in melanoma patients.[28] The group from the Institute of Oncology Ljubljana, Slovenia reported results on 133 tumour nodules in 10 melanoma patients. Eighty-two tumour nodules were treated with electrochemotherapy using cisplatin given intratumourally, 27 tumour nodules were treated with cisplatin intratumourally, 2 tumour nodules were treated with electric pulses alone and 22 tumour nodules were untreated. The untreated nodules and the nodules that were treated with electric pulses alone were subsequently treated with electrochemotherapy. A significant potentiation of antitumour effectiveness of cisplatin was demonstrated in electrochemotherapy treated nodules ($p < 0.001$), whereas exposure of tumour nodules to electric pulses without cisplatin had no effect on tumour growth. Four weeks after therapy 78% objective responses were obtained in the electrochemotherapy group with 68% complete responses, and 38% objective responses were obtained in cisplatin group with 19% complete responses. At 124 weeks of follow up, a 77% control rate of tumour nodules treated by electrochemotherapy was observed, compared to 19% of those that were treated with cisplatin only. These data were confirmed by successive study on 14 melanoma patients where 211 tumour nodules were treated by electrochemotherapy with cisplatin given intratumourally.[16] Objective response rate was 81%, with 70% of complete responses of the electrochemotherapy treated nodules. Based on these studies cisplatin was recognised as one of the two drugs that can be used in electrochemotherapy with intratumoural drug injection (Tables 1 and 2).

The presented studies form the basis for implementation of electrochemotherapy showing that electrochemotherapy can be used in tumours of different histological origin and that those two drugs, namely bleomycin and cisplatin can be successfully employed in combination with electroporation. It was also shown that bleomycin can be administered either intravenously or intratumourally while for the cisplatin, intratumoural administration results in better response compared to intravenous administration. Furthermore, the electrical parameters used in the presented studies proved to be appropriately selected. However, attention has to be paid to the coverage of whole tumour area by electric pulses to obtain electroporation above the threshold values. This topic is further discussed in this issue in article of D. Miklavcic.

Besides these studies that introduced the four possible ways of performing electrochemotherapy; using bleomycin or cisplatin, both given either systemically or locally, other cancer centres have started clinical studies with electrochemotherapy. A group from Chicago, USA reported on successful treatment of head and neck tumours in 10 patients by electrochemotherapy with bleomycin given intratumourally.[6] A group from Mexico City, Mexico performed a phase II study on 15 patients with 38 skin lesions with electrochemotherapy with bleomycin given intratumourally (9 patients with basal cell carcinoma (9 nodules), 2 patients with in-transit melanoma metastases (13 nodules), 2 patients with squamous cell carcinoma of the upper aerodigestive tract metastatic to the skin (2 nodules) and 2 patients with skin metastases from breast cancer (14 nodules)). An objective response was obtained in 98% of the treated nodules. From these, 49% were in complete response.[9] The results of the multicentre study on T1 and T2 squamous cell carcinoma of the oral cavity reported by the group from Vienna, Austria.[10] Twelve patients (12 nodules) were treated using electrochemotherapy with bleomycin given intratumourally. The tumours were surgically removed 4 weeks after electrochemotherapy. Ten surgically excised specimens were completely free of cancer cells, two cases showed viable tumour cells. A phase II, randomised, open label study comparing electrochemotherapy with bleomycin given intratumourally with intratumourally given bleomycin alone was conducted at Sydney Melanoma Unit, Sydney, Australia.[12] The results were in accordance with other studies, 72% of complete responses and 78% of objective responses of electrochemotherapy treated tumour nodules. Additional nodules that were treated with electrochemotherapy out of the study had the same objective response rate (72%) (Tables 1 and 2).

3. Drugs in electrochemotherapy

3.1. *Systemic versus local drug delivery*

Bleomycin and cisplatin were used in electrochemotherapy protocols in two routes of administration, systemic and local. Bleomycin dose given intravenously was in bolus 18000–27000 IU/m^2 which is a low dose and does not induce antitumour effectiveness, however, when combined with application of electric pulses, it results in 78% (50–100%) objective response rate (Tables 1 and 2). Electrochemotherapy with intratumourally injected bleomycin in a dose 250–3000 IU/cm^3 resulted in 87% objective response rate (60–100%) which is comparable to intravenous route of bleomycin administration. Predominant type of tumours that were treated in the studies before ESOPE study was melanoma, with objective response rate of 88% by electrochemotherapy with bleomycin given intravenously, whereas electrochemotherapy with bleomycin given intratumourally resulted in objective response rate of 90%. Furthermore, the complete response rate comparing all the treated tumour types was higher for electrochemotherapy with bleomycin given intratumourally 77% compared to electrochemotherapy with bleomycin given intravenously 45% (Tables 1 and 2).

When comparing different routes of cisplatin administration in electrochemotherapy with cisplatin, as mentioned before, the published studies demonstrated that electrochemotherapy with cisplatin given intratumourally results in much higher objective response rate (83%) compared to cisplatin given intravenously with 48% objective response rate[27,28] (Tables 1 and 2).

Furthermore, it has to be stressed that intratumoural injection of cisplatin alone results in certain local tumour

control (38% objective responses),[28] compared to intratumoural injection of bleomycin where most of the studies demonstrated no local tumour control[21,22] or some local tumour control (32%), if using higher bleomycin doses.[12]

3.2. *Electrochemotherapy with bleomycin versus cisplatin*

Which drug is more effective in electrochemotherapy? This question can not be answered based on previous studies, since no study compared these two forms of electrochemotherapy. However, based on the published studies, the results can be compared only for the melanoma patients (Table 1). Overall treatment responses are comparable, objective response rate of the tumours treated by electrochemotherapy with bleomycin given intratumourally was 90%, with complete response rate of 77%, whereas in the study with electrochemotherapy with cisplatin given intratumourally objective response rate was 83% with complete response rate in 74%. In electrochemotherapy with intravenously given drugs, bleomycin was demonstrated to be more effective than cisplatin.

3.3. *Comparison of the results to the ESOPE study*

The ESOPE study was launched in order to evaluate and confirm efficacy and safety of electrochemotherapy with bleomycin or cisplatin on cutaneous and subcutaneous tumour nodules of patients with melanoma and other malignancies in a multicentre study with an unified treatment protocol. ESOPE study has demonstrated comparable results to previously mentioned studies, confirming efficacy of electrochemotherapy on different tumour types. In addition, no difference was obtained in treatment effectiveness between electrochemotherapy protocols with bleomycin or cisplatin when administered intratumourally, as reported in this issue in the article of M. Marty and G. Sersa et al.

4. Treatment advantages

Electrochemotherapy is used for the treatment of cutaneous and subcutaneous tumour nodules of any type of malignancies. The advantages for electrochemotherapy can be summarised:

4.1. *Effectiveness in tumour nodules of different histologies*

Melanoma was the predominant tumour type in the clinical studies;[21,28] however, there are several reports demonstrating effectiveness of electrochemotherapy on other types of recurrent tumours or metastases, like breast carcinoma,[29] head and neck tumours,[10] squamous cell carcinoma,[21] basal cell carcinoma[22] and others in more sporadic reports.[21,26] The objective response rate of non-melanoma tumours was the same as of melanoma tumours 81%, which indicates on equal effectiveness of electrochemotherapy on different tumour types. The rationale for the obtained results is simple, either bleomycin or cisplatin, when reaching intracellular targets, exert their cytotoxic action, if sufficient amount of the drug is present in the cells. Since electric pulses induce electropermeabilisation of the cells, in electrochemotherapy more drug is able to reach its intracellular targets, the cell DNA, which explains the higher efficacy of these drugs in association with application of electric pulses to the tumours. Besides this principal underlying mechanism of antitumour effectiveness of electrochemotherapy, other mechanisms are also involved and are discussed in this issue in the article of L.M. Mir. Based on the preclinical and clinical data, electrochemotherapy can be used in treatment of single or multiple tumour nodules of different histology in the cutaneous and subcutaneous tissue.

4.2. *Minimal side effects*

Electrochemotherapy is easy and quick (~25 min) to perform, in majority of cases on out-patient basis (as clearly stated in the SOP). Therefore, it has minimal burden to the patients, since in most case its effectiveness was demonstrated after a single treatment. However, it could be repeated with equal antitumour effectiveness, if the tumour nodules recur or if new tumour nodules emerge. After treatment no specific care or dressing of the treated nodules is required. All these aspects, and the fact that electrochemotherapy can be performed also in patients with contraindications for surgical treatment or radiation therapy and in elderly patients, provide evidence that electrochemotherapy has substantial impact on quality of life in cancer patients with progressive disease. Furthermore, electrochemotherapy is performed with low doses of bleomycin or cisplatin therefore no systemic side effects were observed.

4.3. *Simple application*

Electrochemotherapy can be performed in general or local anaesthesia. In either of the procedures it is a simple procedure that can be, in the case of local anaesthesia, performed on an out patient basis. No extra technical skills are needed to perform the treatment, an 1 day training session is sufficient to perform the treatment according to the prepared SOP. Therefore, it is a procedure that can be performed also in developing countries and small hospitals, where other standard treatments are not readily available. In comparison with the complexity of other local or regional treatments like radiotherapy, isolated extremity perfusion and infusion it is much more simple.[33]

4.4. *Repetitive treatment*

Electrochemotherapy is an effective treatment when sufficient drug concentration is obtained in the tumour nodules and the whole tumour volume is adequately covered by application of electric pulses, so that most of the tumour cells are electroporated. In the case of bigger tumour nodules that are not covered by electric field in single run of electric pulse application, several applications of electric pulses are required. In such cases viable tumour cells may remain, therefore recurrent or remaining tumour mass must be retreated. Electrochemotherapy is very effective in repetitive treatments as demonstrated in several clinical cases.[21,28] The treatment can be repeated in 3–6 weeks interval with the same treat-

ment effectiveness as in the previous treatment. In our study, in the case of squamous cell carcinoma in the neck region, the exophytic part of the tumour was treated in eight sessions over a 3-week period. Six months after the start of the treatment, complete response of the treated nodule was obtained and cytologically confirmed. This indicates also that even after eight sessions, electrochemotherapy with cisplatin did not result in acquired cisplatin resistance in the treated area.[23] Therefore, these results demonstrate that electrochemotherapy can be repeated resulting in good antitumour effectiveness without development of resistance to chemotherapeutic drugs.

4.5. *Effectiveness in tumours emerging in pre-treated areas*

Electrochemotherapy was so far tested in patients with progressive disease, where other standard treatment procedures have failed or were exhausted. In some cases the recurrent tumour nodules were in previously irradiated areas[23] or in the area of the surgical field of the previously removed nodules.[21] Clinical data demonstrated effectiveness in most of these cases, regardless of being in previously irradiated areas or in previously resected areas, or in the skin flap. In such cases standard interventions are no longer possible and electrochemotherapy provides treatment of choice for these tumours (Fig. 1).

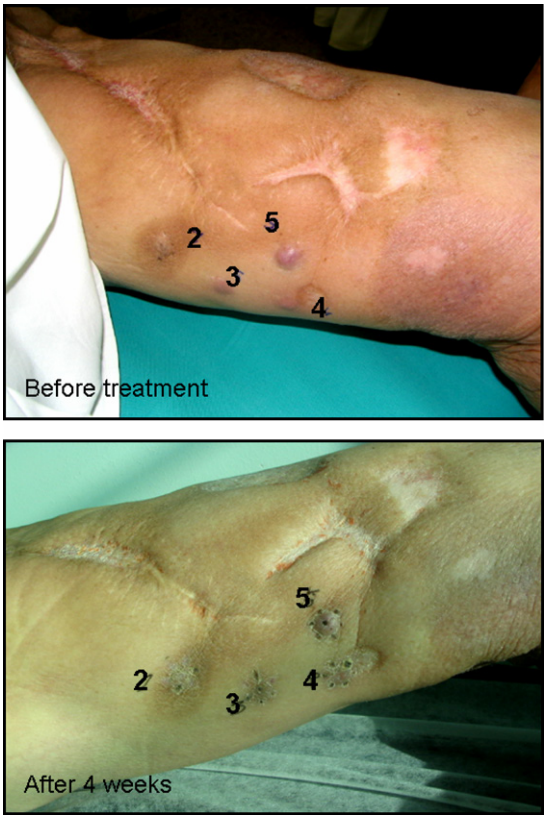

Fig. 1 – Antitumour effectiveness of electrochemotherapy with bleomycin given intravenously. Electric pulses to melanoma nodules on the leg were applied by hexagonal centred electrodes. The melanoma nodules were located in surgically pre-treated area. Complete and partial responses of the treated nodules are visible after single electrochemotherapy session, with good cosmetic effect, without scaring of the treated area.

5. Clinical uses

5.1. *Palliative treatment*

In cancer patients with progressive disease (stage IV melanoma), due to the lack of suitable treatment that would prolong overall survival, the objective of the treatment should be improving quality of life during terminal phase. Especially, for the in-transit metastases in extremities, the surgical treatment sometimes requires amputation of the limb, which is causing severe disability and physiological burden to the patient. Radiotherapy and chemotherapy options are also absent or very limited because of the number of metastases, low effectiveness or previous treatment. Palliative treatments in these cases are very scarce and mainly represented by isolated limb perfusion and infusion. Both of these treatments require highly skilled surgeons as well as adequate facilities that can not be easily translated to other cancer centres where this experience does not exist. Therefore, electrochemotherapy might represent an alternative to other standard treatments, for example surgery, radiation therapy due to its simplicity, short duration of the treatment and tissue preservation.[21,23]

5.2. *Neodjuvant treatment*

Electrochemotherapy can be used as neoadjuvant treatment in form of cytoreductive therapy before conventional treatment. A case of anal melanoma was reported where two repetitive electrochemotherapy treatments were used as cytoreductive treatment enabling surgical resection of anal melanoma with organ and function sparing effect.[30] In addition, treatment of digital chondrosarcoma demonstrated that electrochemotherapy enabled resection of the tumour and bone grafting to fill the bone defect, rescuing the finger from amputation.[11] So far, these are the only cases reported in the literature, but several similar cases can be foreseen where electrochemotherapy could be used as cytoreductive treatment before conventional treatment.

5.3. *Organ and function sparing treatment*

Electrochemotherapy can be performed on all parts of the body including the skull, face, oral cavity and anal sphincter. In certain parts of the body, surgery or radiation therapy can not be performed with organ and function sparing effect. The reports demonstrated that treatment of basal cell carcinoma of the skin on the face, especially in the ears, nose and lips has good antitumour and less disfiguring effect than excisional surgery, therefore being a tissue preserving procedure.[22] The report on treatment of recurrent perineal melanoma has demonstrated that electrochemotherapy provides a means for organ sparing, instead of surgical urethrectomy, which should have been performed with urinary diversion.[31] All these reports and other indications that may be foreseen

demonstrate that electrochemotherapy can be used as organ sparing and function saving treatment.

5.4. *Treatment of haemorrhagic and painful tumour nodules*

The application of electric pulses to the tissues induces a transient, but reversible reduction of blood flow, as reported in preclinical studies. The restoration of the blood flow in normal tissue is much faster than of that in tumours. As the results of that it provides prolonged drug action in the tumours and prevents bleeding. The latter was reported in treatment of haemorrhagic nodules of malignant melanoma where electrochemotherapy was suggested as treatment of choice for the palliation of haemorrhaging skin metastases.[7,8] Furthermore, it was demonstrated that electrochemotherapy alleviated the pain around the tumour location (squamous cell carcinoma of supraglotis) to the extent that the patient no longer required analgesics.[23] Another report on skin metastases originating from bladder cancer reported that electrochemotherapy alleviated pain in painful nodules besides preventing their bleeding.[7] Besides these reports, similar observations were also made in the ESOPE study.

6. Conclusion

Electrochemotherapy is now on the verge of becoming standard treatment of cutaneous and subcutaneous tumour nodules of different malignancies, mainly with palliative intention. However, further progress of electrochemotherapy will continue by developing new electrodes that will enable the treatment of larger tumours and tumours in internal organs. Consequently, the indications for electrochemotherapy will extend in the future.

Acknowledgements

The author acknowledges the financial support of the state budget by the Slovenian Research Agency (Project No. P3-0003) and EU funded project ESOPE (QLK-2002-02003). The author thanks his colleagues and partners in the ESOPE project for criticism of the manuscript.

REFERENCES

1. Mir LM, Belehradek M, Domenge C, et al. Electrochemotherapy, a new antitumor treatment: first clinical trial. *C R Acad Sci III* 1991;**313**:613–8.
2. Belehradek M, Domenge C, Luboinski B, Orlowski S, Belehradek Jr J, Mir LM. Electrochemotherapy, a new antitumor treatment. First clinical phase I–II trial. *Cancer* 1993;**72**:3694–700.
3. Rudolf Z, Stabuc B, Cemazar M, Miklavcic D, Vodovnik L, Sersa G. Electrochemotherapy with bleomycin: the first clinical experience in malignant melanoma patients. *Radiol Oncol* 1995;**29**:229–35.
4. Glass LF, Fenske NA, Jaroszeski M, et al. Bleomycin-mediated electrochemotherapy of basal cell carcinoma. *J Am Acad Dermatol* 1996;**34**:82–6.
5. Rols MP, Bachaud JM, Giraud P, Chevreau C, Roche H, Teissie J. Electrochemotherapy of cutaneous metastases in malignant melanoma. *Melanoma Res* 2000;**10**:468–74.
6. Panje WR, Hier MP, Garman GR, Harrell E, Goldman A, Bloch I. Electroporation therapy of head and neck cancer. *Ann Otol Rhinol Laryngol* 1998;**107**:779–85.
7. Kubota Y, Mir LM, Nakada T, Sasagawa I, Suzuki H, Aoyama N. Successful treatment of metastatic skin lesions with electrochemotherapy. *J Urol* 1998;**160**:1426.
8. Gehl J, Geertsen PF. Efficient palliation of haemorrhaging malignant melanoma skin metastases by electrochemotherapy. *Melanoma Res* 2000;**10**:585–9.
9. Rodriguez-Cuevas S, Barroso-Bravo S, Manza-Estrada J, Cristobal-Martinez L, Gonzalez-Rodriguez E. Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. *Arch Med Res* 2001;**32**:273–6.
10. Burian M, Formanek M, Regele H. Electroporation therapy in head and neck cancer. *Acta Otolaryngol* 2003;**123**:264–8.
11. Shimizu T, Nikaido T, Gomyo H, et al. Electrochemotherapy for digital chondrosarcoma. *J Orthop Sci* 2003;**8**:248–51.
12. Byrne CM, Thompson JF, Johnston H, et al. Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). *Melanoma Res* 2005;**15**:45–51.
13. Bloom DC, Goldfarb PM. The role of intratumour therapy with electroporation and bleomycin in the management of advanced squamous cell carcinoma of the head and neck. *Eur J Surg Oncol* 2005;**31**:1029–35.
14. Heller R, Gilbert R, Jaroszeski MJ. Clinical applications of electrochemotherapy. *Adv Drug Deliv Rev* 1999;**35**: 119–29.
15. Gothelf A, Mir LM, Gehl J. Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation. *Cancer Treat Rev* 2003;**29**:371–87.
16. Sersa G, Cemazar M, Rudolf Z. Electrochemotherapy: advantages and drawbacks in treatment of cancer patients. *Cancer Therapy* 2003;**1**:133–42.
17. Glass LF, Pepine ML, Fenske NA, Jaroszeski M, Reintgen DS, Heller R. Bleomycin-mediated electrochemotherapy of metastatic melanoma. *Arch Dermatol* 1996;**132**:1353–7.
18. Heller R, Jaroszeski MJ, Glass LF, et al. Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. *Cancer* 1996;**77**:964–71.
19. Domenge C, Orlowski S, Luboinski B, et al. Antitumor electrochemotherapy: new advances in the clinical protocol. *Cancer* 1996;**77**:956–63.
20. Glass LF, Jaroszeski M, Gilbert R, Reintgen DS, Heller R. Intralesional bleomycin-mediated electrochemotherapy in 20 patients with basal cell carcinoma. *J Am Acad Dermatol* 1997;**37**:596–9.
21. Mir LM, Glass LF, Sersa G, et al. Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. *Br J Cancer* 1998;**77**:2336–42.
22. Heller R, Jaroszeski MJ, Reintgen DS, et al. Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. *Cancer* 1998;**83**:148–57.
23. Sersa G, Stabuc B, Cemazar M, Jancar B, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: potentiation of local cisplatin antitumour effectiveness by application of electric pulses in cancer patients. *Eur J Cancer* 1998;**34**:1213–8.
24. Sersa G, Cemazar M, Rudolf Z, Fras AP. Adenocarcinoma skin metastases treated by electrochemotherapy with cisplatin combined with radiation. *Radiol Oncol* 1999;**33**:291–6.
25. Rebersek M, Cufer T, Rudolf Z, Sersa G. Electrochemotherapy with cisplatin of breast cancer tumor nodules in male patient. *Radiol Oncol* 2000;**34**:357–61.

26. Sersa G, Cufer T, Cemazar M, Rebersek M, Rudolf Z. Electrochemotherapy with bleomycin in the treatment of hypernephroma metastasis: case report and literature review. *Tumori* 2000;**86**:163–5.
27. Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: the systemic antitumour effectiveness of cisplatin can be potentiated locally by the application of electric pulses in the treatment of malignant melanoma skin metastases. *Melanoma Res* 2000;**10**:381–5.
28. Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: clinical experience in malignant melanoma patients. *Clin Cancer Res* 2000;**6**:863–7.
29. Rebersek M, Cufer T, Cemazar M, Kranjc S, Sersa G. Electrochemotherapy with cisplatin of cutaneous tumor lesions in breast cancer. *Anticancer Drugs* 2004;**15**:593–7.
30. Snoj M, Rudolf Z, Cemazar M, Jancar B, Sersa G. Successful sphincter-saving treatment of anorectal malignant melanoma with electrochemotherapy, local excision and adjuvant brachytherapy. *Anticancer Drugs* 2005;**16**:345–8.
31. Kubota Y, Tomita Y, Tsukigi M, Kurachi H, Motoyama T, Mir LM. A case of perineal malignant melanoma successfully treated with electrochemotherapy. *Melanoma Res* 2005;**15**:133–4.
32. Allegretti JP, Panje WR. Electroporation therapy for head and neck cancer including carotid artery involvement. *Laryngoscope* 2001;**111**:52–6.
33. Vrouenrats B, Kroon BBR, Nieweg OE, Thompson JF. Isolated limb perfusion for melanoma. In: Thompson JF, Morton DL, Kroon BBR, editors. *Textbook of melanoma*. London: Martin Dunitz; 2004. p. 410–28.