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Electrochemotherapy for Treatment of Cutaneous Breast Cancer Metastases: A Review

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ABSTRACT

Background: Electrochemotherapy is a relatively new technique in the treatment of skin metastases that are not amenable to conventional therapy. Its use in breast cancer is now established in many European centers.

Methods: Published literature of electrochemotherapy in terms of its scientific basis, current clinical practice of breast cancer treatment providers, as well as the future directions for the technology has been reviewed.

Results: Collective global experience of the last 10 years has demonstrated Electrochemotherapy is a safe, well-tolerated and effective treatment of cutaneous breast cancer metastases and good outcome characteristics have been identified. However, successful treatment requires appropriate patient selection.

Conclusions: Electrochemotherapy is now established as a standard of care for cutaneous metastases. Its future use may extend to gene therapy and the treatment of visceral tumors.

Introduction

Cutaneous metastases from breast cancer occur in about 2% of patients and account for only 0.7-0.9% of all metastases.[3,4] However breast cancer metastases to the skin represent 51% of all of skin metastases and often this is the only manifestation of disease progression in these patients.[4] Until recently, this rare presentation has been difficult for both the surgeon and oncologist to treat; often the surgical options are limited due to the extent of skin surface involved. Systemic chemotherapy and radiotherapy provides effective palliation. However, repeated cycles of treatment leads to chemo-resistance and radiotherapy cannot be used in previously irradiated areas.

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Patients can become increasingly symptomatic, if the skin lesions are inadequately treated. Lesions become necrotic and ulcerated and their management relies heavily on nursing resources. Electrochemotherapy (ECT), a novel treatment, which is well tolerated, repeatable and effective, provides an additional treatment option for cutaneous metastases. Electrochemotherapy (ECT) is the administration of a low dose chemotherapeutic agent that is non-permeable or poorly permeable in combination with high intensity electrical pulses of short duration to facilitate targeted drug delivery into tumour cells. Exposure of tumour cells to the pulses of electrical fields in itself can cause apoptosis by the formation of nano-pores in the cell membrane, a process known as electroporation.[5,6]

Methods

A pubmed search was conducted using keywords 'electrochemotherapy and breast cancer'. In addition publications by InSpECT was also considered. InspECT is an international collaboration formed in 2008 providing a forum and infrastructure for medical teams working with electrochemotherapy to be able to meet and discuss issues related to

its use.[7]

An international database facilitated by this organization has allowed collaborative publications. All data is monitored according to GCP procedures.[7] Publications relating to electrochemotherapy were included in this review, if they were published in English and were published from centers with experience of treatment delivery. Clinical publications were selected if they presented a retrospective study, multi-center or single prospective observation study. Case study publications were not included. Scientific publications were considered for inclusion, if they were review publications or were cited in review publications and were relevant to breast cancer.

Results

Scientific basis for electrochemotherapy

When a cell is exposed to an external electrical field for a short duration, transient thinning of the phospholipid bilayer occurs with the formation of nano-pores allowing passage of extracellular substances (Figure 1).[8] The first practical demonstration of this phenomenon was the technique of DNA transfection of bacteria by applying a current from a laboratory generator.[9] The development and production of square wave generators, that allowed precision of treatment delivery in terms of the number of pulses and their characteristics facilitated electropermeabilization of a large population of cells without lethal cytotoxicity.[10]

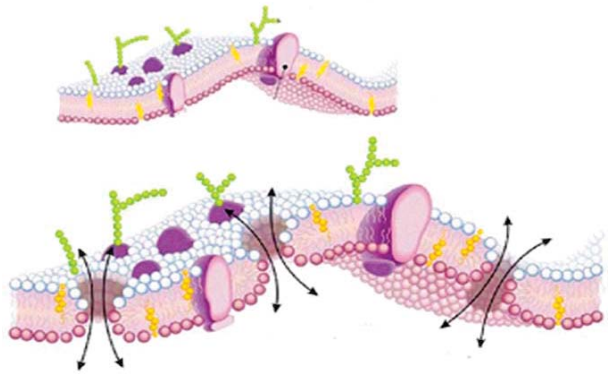

Figure 1. Mechanism of electroporation: high intensity electrical pulses applied to cells result in transient nano-pore formation (as indicated by the arrows) allows impermeable molecules molecules to enter the cell.[51]

The initial in-vitro observations by Mir *et al.* that lead to the development of this technology as a viable treatment showed that bleomycin a established cancer medication which is poorly permeable and normally absorbed by a receptor mediated endocytosis could enter tumour cells by electropermeabilization.[9-11] Low molecular concentrations of bleomycin in the intracellular environment, was highly toxic to tumour cells. Therefore, the combination of electroporation, with Bleomycin increased its potency several hundred times in vitro.[12]

There are several theories explaining mechanism of how this occurs. This includes the phase transient model, the denaturation model and the electroporation model.[13-15] The accepted understanding of the process of reversible electroporation that occurs in ECT is spontaneous, but transient pore formation occurs in the cell membrane in response the high intensity electrical fields. These nano-pores retain sufficient stability to allow relatively large molecules to become intracellular. However the presence of these pores are of extremely short duration and the cell membrane returns to it normal structure.[5,16]

An important secondary effect of the high intensity field demonstrated by in vivo studies is local vasoconstriction and hypoxia and endothelial disruption.[17-19] ECT results in a reduction in tumor blood flow that occurs in 2 phases. A short-lived episode when the electric pulses are delivered resulting in a 'vascular lock' around the tumor cells that prevents washout of the cytotoxic agent and further concentrates the cytotoxic agents in the tumor cells.[19, 20] Subsequent disruption of the endothelial cytoskeleton and intracellular junctions results in a change in the configuration of the surface of the endothelium. This leads to an impaired barrier function and interstitial edema resulting in decreased intravascular pressure and compromised blood flow. Repair of the endothelium is slow and a reduction in blood flow in feeding tumor vessels in observed causing severe hypoxia to the tumor cells evident several days after treatment with ECT.[20]

Characteristics of agents that could be effective in ECT are those that are hydrophilic, with molecular structures will not allow entry into cells by diffusion or by transport systems in the cell membrane (Figure 2).[21] Several types of chemotherapeutic agents have been tested for their suitability for ECT. These include the anthracycline group (daunorubicin, doxorubicin and adriamycin), the polypeptide anti tumour antibiotics, the actinomycines group (actinomycin D, mitomycin C), Vinca alkaloids (vinblastine, vincristine) etoposide, paclitaxel, cyclophosphamide, carboplatin, cisplatin and bleomycin.[21] However only ciplatin and bleomycin have been found to have significant potentiation of their activity. Cisplatin has its action potentiated from 10 to 80 fold by electroporation of cells , while Bleomycin, has its action potentiated between 300 and 700 in vitro (Figure 2).[12] In vivo investigations in different animal models and various tumors using ECT with either Cisplatin or bleomycin have lead to further understanding of how clinical treatment could be optimised.[21-23] The mode of drug delivery was found to effective in both intravenous injection as well as intratumoural injection; the caveat for this is intratumoral treatment requires almost immediate electroporation following drug delivery.[23] In contrast, intravenous injection route of delivery

allows a short delay before electroporation needs to commence.[23] Effective electroporation depends on the intensity of the electric field and the devices used for application to the tumor. Sub-dermal are tumours best treated with needle electrodes; superficial tumors are effectively treated with an electrode plate. In addition in vivo studies have shown that the electrical fields optimises tissue distribution.[21,24]

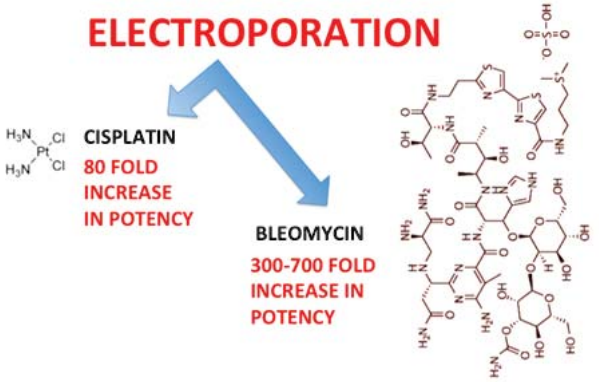

Figure 2. Chemotheraputic agents suitable for ECT: agents that are hydrophilic, impermeable at low concentrations and demonstrate increased potency after electroporation are suitable. Bleomycin and cisplatin have demonstrated the greatest potency.[52, 53]

Electrochemotherapy and breast cancer

The clinical use of ECT was pioneered in the European Union with the first cases treated in the Institute Gustave Roussy, in France and Institute of Oncology, Ljubljana, Slovenia in the 1990s.[25] Since then its use in the treatment of breast cancer skin metastases is well established throughout Europe with the largest number of published breast cancer cases treated in Denmark, Germany, Sweden, Slovenia and Italy.

In 2013, The National Institute of Clinical Excellence (NICE, UK) recommended its use in skin metastases including breast cancer.[26] Prior to this, the first center in the UK to start using ECT was James Cook University Hospital, Middlesborough, in 2010. Then, 6 other hospitals in the UK including our institution also started using the technology. ECT was used to treat patients when all other treatment modalities were unsuccessful or prohibitive. Currently, there are more than 15 centers in the UK offering this treatment. Our Institution is a designated center solely for the treatment of cutaneous metastases from breast cancer in the United Kingdom.[27]

The European Standard Operating Procedures of Electrochemotherapy (ESOPE) study in 2006 recruited 62 patients across 4 cancer centres in France, Ljubljana, Denmark and Ireland.[28] It evaluated and confirmed the efficacy and safety of ECT using bleomycin and cisplatin. This prospective non-randomised study enrolled patients with progressive cutaneous and subcutaneous metastases of any histologically proven cancer. They found an objective response rate of 85% achieved on the ECT treated nodules, regardless of tumor histology. They demonstrated ECT is not limited to non-irradiated skin, as 85 of the 171 nodules treated in the study were in previously irradiated skin. The procedure could also be performed under local anaesthetic for small areas.[28] The ESOPE study standardised the operating procedures for ECT a highly effective and safe approach for the treatment of skin metastases. Patients reported only minor and acceptable side effects. Indeed, 93% said they would be willing to accept the treatment next time, if indicated. Furthermore, it is quick and easy to perform.[11] The results of the study was particularly pertinent to treatment of breast cancer skin metastases, as, 27 patients out of 63 patients included in the study were confirmed to have cutaneous metastases form breast cancer.

Outcome of ECT treatment in breast cancer

A number of studies since then have shown ECT can induce partial or complete response of nodules to the therapy for breast cancer related cutaneous metastases.[29-37] (see Table 1). Specifically, lesions that are associated with bleeding or skin ulceration may benefit from this treatment that would otherwise be refractory to treatment. The ESOPE study demonstrated that, ECT is an effective treatment for elderly patients for whom surgery is not possible, as 16 patients (39% of all treated patients) were over 75 years old.[28] Subsequent publications by Campana *et al.* have also confirmed this finding; elderly patients showed significantly higher complete response rate above the age of 70 compared to patients below this age ($p<0.01$) as shown in table 2.[36, 38] The only justification for patient non- selection in this age group, would be, poor performance status and frailty. Elderly patients are more likely to discontinue treatment early and experience more post-treatment symptoms.[33] The largest published study consisting of 125 breast cancer patients treated with ECT, performed by Cabula *et al.* (2015), showed complete response in 58.4%, with overall response rate of 90.2%.[37] This was a multicenter retrospective study with 113 patients evaluated initially and after at 2 months, with median follow up of 5.9 months. Multivariate analysis of patients and tumors characteristics indicated small tumor size (<3cm), absence of visceral metastases, estrogen receptor positivity and KI-67 positivity were all associated with complete response.[37] Table 2 summarizes these findings. These results suggest that patient selection may be further refined and ECT would be more beneficial, if offered early at first presentation of skin metastases, although the presence of visceral metastases is not a contra-indication to treatment. ECT does not influence disease progression and at present is used as a replacement for other palliative measures. A recent meta-analysis of skin-based

treatment for cutaneous metastasis in advanced cancer by Spratt *et al.*, has demonstrated ECT has low toxicity and comparable outcome to other treatments, including radiotherapy.[39] ECT provides an alternative treatment for patients that have irradiated skin, and an option when all other therapies have failed. One of the most promising aspects of ECT is its unique ability to selectively kill tumor cells without

Table 1. Response rates of breast cancer skin lesions treated with electrochemotherapy in the published literature.

Reference	Year	No. Patients	No. Nodules	Typechemo-therapy	CR	SD/UR	PR	NR
Heller[29]	1995	1	2	IV Bleomycin	2/2 (100%)		0/2 (0%)	0/2 (0%)
Rodrigues-Cuevas[30]	2001	2	14	IT Bleomycin	8/14 (58%)		6/14 (42%)	0/14 (0%)
Rebersek[31]	2004	6	12	IT Cisplatin	4/12 (33%)		8/12 (67%)	0/12 (0%)
ESOPE[28]	2006	61*	58*	IV +IT Bleomycin, IT Cisplatin	73.7%*		11.3%*	14%
Larkin[32]	2007	15**	100	IV / IT Bleomycin	63%	3% (UR)	20%	7%*
Campana[33]	2009	11	174	IV / IT Bleomycin	43%*		50%*	7/25 (28%)
Madero and Parez[34]	2011	25			11/25 (44%)		7/25 (28%)	1/12 (~8%)
Matthiessen[35]	2012	17	1-5 per patient	IV /IT Bleomycin	1/12 (~8%)	9/12 (75%)	1/12 (~8%)	
Campana[36]	2012	35	15/20***	IV Bleomycin	19/35 (54.3%)	3/35 (8.6%)	13/35 (37.1%)	
Campana[38]	2014	55	55	IV Bleomycin	22/55 (40%)	7/55 (12.7%) (SD)	26/55 (47.3%)	
Cabula[37]	2015	125	1-5 per patient	IV /IT Bleomycin	58.4%	0.9% with disease progression + 7.1% stable disease	31.8% + 1.8% with disease progression	

This table only refers to the breast cancer patients in each study. No. nodules refers to those treated with ECT. IV: intravenous; IT: intratumoral; CR: complete response; PR: partial response; SD/UR: unknown response; NR: no response; SD: stable disease
** figures for all cancers (response rates not separated into those specifically for breast cancer) with breast cancer patient in a sub-group of 27 patients and accounting for 58 nodules in the ESOPE study, **1 patient was not treated, one was lost to follow-up, ***15 nodules and 20 plaques in the cohort*

Table 2. Characteristics that have been shown to effect outcome of ECT treatment

Tumor /treatment Characteristic	Prognostic value for outcome	Study size (n)	P value[Reference]
Size 3 cm or less	Associated with CR and LPFS	125	$p < 0.001$ LPFS $P = 0.008$[35]
Size greater than 3 cm	Risk of prolonged post operative pain	125	$P = 0.008$[35]
ER receptor positive	Associated with CR	125	$P = 0.016$[35]
Ki-67	Associated with CR	125	$P = 0.02$[35]
Absence of visceral metastases	Associated with CR	125	$P = 0.001$[35]
Breast cancer subtype: Luminal A*	Associated with CR	125	$P = 0.02$[35]
Irradiated skin	No difference for CR	61*	$P > 0.05$[26]
Current intensity > 5 Amps	Risk of post operative pain	120	$P < 0.0001$[42]
Irradiated skin	Risk of post operative pain	120	$P = 0.014$[42]
Pre-existing pain	High risk of post operative pain	120	$P < 0.0001$[42]
Age over 70	Associated with CR	55 (28)**	$P = 0.023$[42]
Patients with poor performance status at any age	May result in poor outcome for tumor response	55	$P = 0.048$[42]

** Breast cancer classification based on gene expression. Subtype luminal A is estrogen receptor (ER)–positive. Luminal A cancers are low grade, tend to grow fairly slowly, and have the best prognosis,** 28 patients in this study had breast cancer skin metastases and age over 70*

harming normal surrounding tissue as is targeted by the application directly over the lesions to be treated. It is cost-effective, having an incremental cost effectiveness ratio of €1571 with an average cost per achieved response of €1901 (compared to €2007 for radiotherapy and €2851 for combined hyperthermia, chemotherapy and radiotherapy).[40]

Patient selection and treatment considerations

Clinical treatment with ECT has been performed most frequently in patients with advanced metastatic cancer in whom the possibility of standard treatment has been exhausted.[31, 41, 42] NICE guidelines in the U.K. recommends that patients should be considered for ECT, if conventional therapies have been used and are no longer effective, or if the patient cannot have conventional treatment.[26] In our practice, patients with breast cancer skin metastases are assessed through the multi-disciplinary team with regard to their completion of conventional treatment, absence of visceral metastases or their relative stability in the presence of progressing cutaneous disease. As bleomycin is the chemotherapeutic agent of choice, relative and absolute contraindications to its use such as pulmonary fibrosis or severe chronic obstructive airways disease are also contra-indications for ECT unless cisplatin is used instead. Patients should not be taking medications, which increase the risk of life threatening haemorrhage at the time of ECT. Other important considerations to be assessed at the pre-treatment consultation include the patient's general health, mobility, general fitness and pre-existence of pain at the site of cutaneous lesions. Patients with life expectancy less than 3 months should not be considered for treatment. Table 3 summarises the indications and relative contra-indications for ECT. Pre-treatment investigations include staging CT imaging and bone scan to exclude visceral disease progression, which would be an indication for further systemic treatment. Lung function tests are necessary to obtain baseline observations prior to treatment with bleomycin. Post treatment this should be repeated, if further treatments are planned or if patients become symptomatic.

Patients at our institute are given gabapentin prior to their surgery and this is continued for a period of a month post-operatively or longer according to symptoms, to reduce the sustained discomfort that occurs from the muscle stimulation a side-effect of the electrical pulses. In our institute, patients are usually admitted on the day of treatment and discharged the following day, unless symptomatic. Patients referred from outside the catchment area or with medical conditions e.g. on warfarin therapy require admission for optimisation prior to treatment.

ECT can be delivered under both general and local anaesthetisia; however due to the type of lesions and their distribution, all patients treated so far at our institute were given general anaesthesia.[28] Due to the risk of potential risk of pulmonary fibrosis from bleomycin, patients are anaesthetised with inspired oxygen concentrations between 28-32%. If large

Table 3. Patient selection for electrochemotherapy and pre-treatment considerations.[54]

Indications for treatment	Cutaneous and subcutaneous metastases of skin and non-skin origin and melanoma in the presence or absence of disseminated disease WITH or WITHOUT: bleeding, pain and ulceration.
Treatment contra- indications	Patients should not be referred for electrochemotherapy, if they have pre-existing conditions that would become significantly worse or life threatening, if treatment was performed. This includes: 1. Symptomatic and/or rapidly progressive non-cutaneous metastasis are relatively contraindicated and treatment suitability will be decided by Multi Disciplinary Team 2. Allergic reactions to bleomycin (BLM) or cisplatin (CDDP) 3. Cumulative dose of 250 mg BLM/m2 4. Peripheral neuropathy >grade 2 5. Coagulation anomalies whose severity is such as to be life threatening or deemed unsuitable for electrochemotherapy by the MDM (Multidisciplinary team meeting) 6. Chronic renal dysfunction (creatinine> 150micromol/lit) 7.Arrhythmia/Pacemaker* 8. Epilepsy 9. Patients who are currently pregnant or lactating are not suitable for electrochemotherapy. 10. They should not have any inter-current infection at the time of electrochemotherapy.
Pre-treatment investigations/ assessments	Eligible patients should have the following investigations within 3 weeks of referral date and preferably at least 3 weeks after any chemotherapy treatment: 1. Full Blood Count, 2. Urea & Electrolytes AND Creatinine 3. Liver Function Tests & Clotting 4. Pulmonary Function Tests 5. STAGING contrast CT (thorax/abdomen/pelvis) AND whole body bone scan within 3 months of treatment date. 6.The MRSA status of the patient should be known and if positive, appropriate treatment should have been given. Eligible patients should be reviewed in a joint clinic by the oncologist and surgeon who will perform the electrochemotherapy. This should usually take place within 4 weeks prior to treatment date.

** Electrochemotherapy may be performed in areas other than directly over and around the pacemaker with cardiology supervision or external pacing. Pre-treatment cardiology opinion is essential.*

areas are to be treated, intra-operative fentanyl or morphine infusions are given. These may be continued as required post treatment. Intravenous bleomycin is given under general anaesthesia (Figures 3 to 7) and after 8 minutes, ECT is commenced. The dose of bleomycin is pre-calculated by the medical oncologist according to the Dubois formula[43] and is based on height and weight measurements; it is much lower than the standard therapeutic doses used in systemic chemotherapy. The choice of the electrodes is determined by the size and extent of the lesions, with 3 types of electrodes currently being employed; these are linear row needle electrodes, hexagonal array needle electrodes and plate electrodes. The linear row electrodes more effective with smaller less extensive lesions, while the hexagonal electrodes used typically in extensive diffuse lesions.

Prior to treatment, careful documentation of the size of each lesion to be treated and the dimensions of the field of treatment supplemented by photographs allow objective assessment of outcome. ECT is performed, by inserting the electrode needles subcutaneously into the lesions to be treated, and then firing the electrodes generated pulses (Figures 3-7). This is then also applied up to a centimetre circumferentially around the lesions. The treatment duration is limited to a maximum of 40 minutes reflecting the fall in concentration of bleomycin, which becomes sub-therapeutic after this. At the end the procedure, the wounds are dressed with gauze soaked with local anaesthetic gel. Following treatment, patients are usually observed for 24 hours and given standard surgical nursing care. Most patients are discharged with simple analgesics. Post treatment wound review usually occurs at 4-6 weeks post ECT with outcome review at 3 months. In our center, we have only treated patients with breast cancer skin metastases; the practice in other centers that also treat other types of skin lesions such as melanoma and other skin cancer metastases will invariably have differences in practice to what comprises optimal treatment. Typically in some European centers, patients are treated for small lesions without need for post-treatment admission to hospital, while treatment of extensive chest lesions may require a period of admission in hospital for post treatment analgesia. All ECT treatments require a multidisciplinary approach for determining patient selection as well as delivery of treatment. Figures 8 and 9 shows treatment outcome with ECT at our institute.

Figure 3

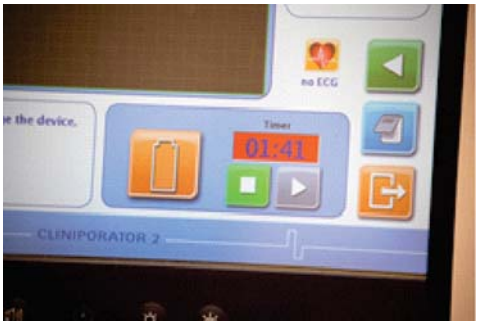

Figure 4

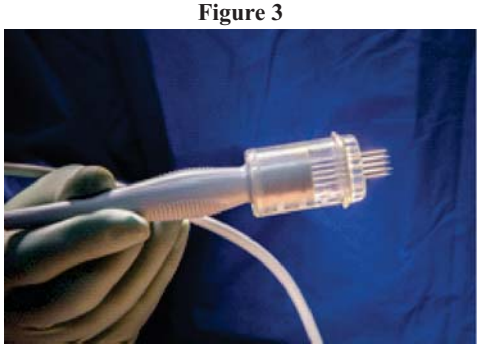

Figure 5

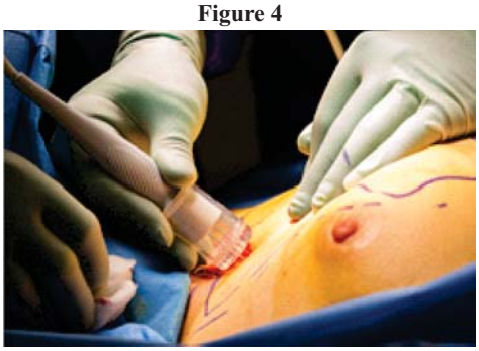

Figure 6

Figure 7

Figures 3 to 7. ECT treatment:[1]
3) Intra-venous bleomycin is given
4) 8 minutes elapsed before ECT treatment
5, 6 and 7) needle electrodes are inserted through the skin directly at the site of the lesions and circumferential area and the electrical impulses fired by a hand/foot pedal.

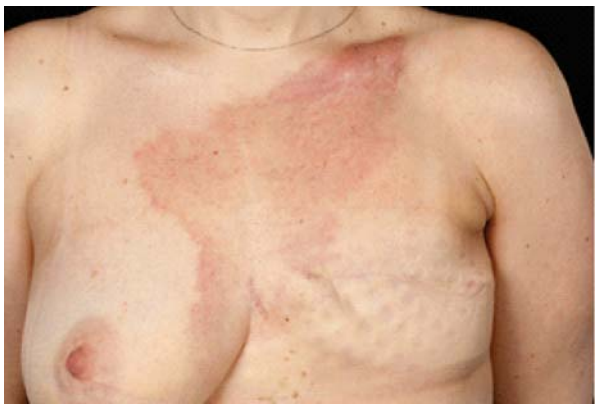

Figure 8

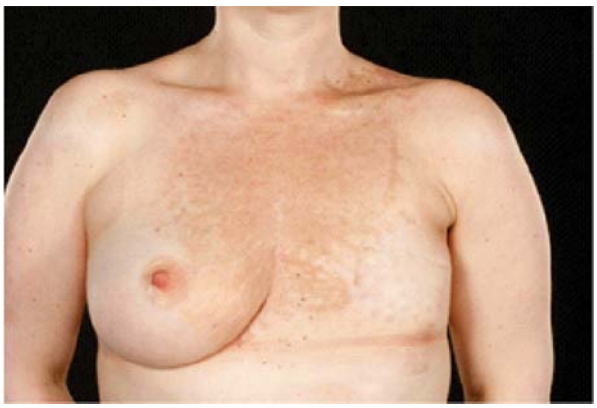

Figure 9

Figure 8 and 9. Electrochemotherapy outcome [1, 2]. Figure 8 Shows chest wall lesions in a 37 year-old patient who was diagnosed with left breast cancer (T3N2M0), which was triple receptor positive. She was initially treated mastectomy and axillary node clearance. She was given chemotherapy and chest wall radiotherapy followed by zoladex and tamoxifen. Three years later she developed liver metastases and a chest wall rash proven to be skin metastases. After second line chemotherapy, the visceral lesions were stabilized; however the chest wall lesions were persistent and extending in area. Figure 9 shows this patient 6 weeks after ECT treatment. There is minimal hyperpigmentation and there was complete response of all treated lesions. She was skin lesion-free for 6 months.

Observed adverse effects and their management

In general, patients who undergo ECT do not have significant adverse symptoms and in our experience and that of the other authors, the majority have minimal symptoms and would be willing to be re-treated.[28, 38, 44] However ECT-related side effects have been identified in breast cancer patients. Hyperpigmentation occurs in the treated areas of all patients who have ECT; but the extent and intensity is variable. Patients with tumour regression are associated with less hyperpigmentation but this finding is not universal. Only in 10% of patients adverse symptoms are severe.[37,44]

Breast cancer patients are more likely to experience post-operative pain (see Table 2).[44] Studies of treatment conducted before 2014 have included pain as a significant side effect; however after this period, the use of new electrodes which cause less fasciculation during treatment; fewer patients at our institute have had persistent pain symptoms after this. A recent review of post-operative pain showed that 74% of patients have little or no pain immediately after treatment and in the immediate follow up period.[44] In most patients pain was experienced as dull aching discomfort, typically appearing by 4-8 weeks after treatment and in most resolving by 12 weeks.[44] This is temporary in most patients, who experience pain and is adequately treated with simple analgesia. However more persistent high intensity pain can occur and may need to be treated with opiate medication. Investigations of factors, which may increase the likelihood of post-operative pain have shown that treatment of the chest wall, or irradiated skin are associated with post-operative symptoms.[44] Patients who already experience pain from their skin lesions are also more likely to be symptomatic.[44] Tumor size and the extent of treatment area are also implicated to post treatment pain; tumors greater than 3 cm and a large surface area of treatment are associated with pain.[44]

Other adverse effects include skin ulceration as a result of necrosis and regression of the tumor following treatment.[44] This may take some time to heal and need repeated debridement and specialist skin care or surgical intervention.[27,44] Excision of the lesion en bloc, and then treatment of the base and circumferential area with ECT, before primary closure, may avoid this problem. In our experience, diffuse infiltration of the skin with tumor may cause post treatment skin loss. In cases where this has occurred, the authors have combined treatment with plastic surgery; initially debridement of the necrotic tissue followed by VAC® dressings to reduce edema and encourage wound healing. Biopsy of the wound bed may be considered first to exclude tumor as this treatment facilitates angiogenesis and if tumor is present, this may stimulate further recurrence.

Bleomycin has been associated with pulmonary fibrosis when used in systemic chemotherapeutic regimens. The dose of bleomycin used in ECT is much lower than the therapeutic dose used in conventional systemic therapy, and due to its relative insolubility has no systemic effect. There has been no cases of bleomycin toxicity in the published series; however repeated treatment may increase this risk. Therefore, careful patient selection and treatment planning with assessment of pulmonary function would be of benefit.

Discussion

The promising objective response rates achieved so far suggest that in the future this therapy may be a treatment option in an earlier phase in the management of breast cancer in conjunction with chemotherapy. This is suggested by findings of

Cabula *et al.* and further refinement of patient selection using favorable characteristics to improve outcome may also be possible.[37] Prospective randomised trial to investigate these possibilities is the next step to advance the use of this treatment.

It is also likely that as the technology develops, it will be used on an even wider range of tumors including those deep within the body. Indeed, endoscopic devices have been shown to be successful against breast cancer cell lines that may be used in the future for inaccessible cancers.[45] Electrical pulses are not limited to use in conjunction with chemotherapy. Electroporation for gene therapy has been demonstrated for melanoma.[46] Direct therapy may generate a direct anti-tumor effect and delivery to alternative sites may lead to the production of cancer vaccines, reduction in tumor angiogenesis, or the induction of tumor cell apoptosis.[46] This immune therapeutic effect may be responsible for the local benefits seen in clinical treatment; however investigation of the immune effects induced by electrochemotherapy in breast cancer are restricted to pre-clinical studies.[47] The electrical pulses in themselves have also been shown to be beneficial. Nanosecond pulsed electric fields (nsPEFs) have been shown to inhibit tumor growth and can target intracellular organelles and has been studied in other cancer cell lines in vitro.[48] Irreversible electroporation (IRE) is a new ablation procedure that uses pulses to provoke permanent permeability of the cells resulting in their death without any thermal effects making it better tolerated than other ablation technologies.[49] ECT may also be used in adjunct to other forms of established treatment such as radiotherapy; although hypoxia causes radio-resistance, ECT agents have also radio-sensitizing effects that are further amplified during ECT.[50] This advantage may be utilized in the development of combined therapeutic treatment planning.

In conclusion, ECT has already been established as a standard of care for the treatment of breast cancer skin metastases and compares favourably with other skin treatments. Its potential for expansion from its current rather limited use to first line, widespread treatment is supported by recent publications.

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