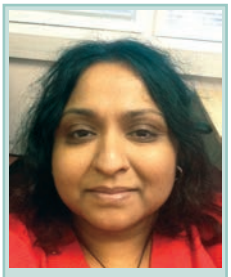
Electrochemotherapy



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Breast cancer is one the leading causes of mortality worldwide and incidence is rising. Although it is an increasingly treatable disease, at least 10% will experience loco-regional recurrence and 24% of these will suffer cutaneous manifestations at some point which can be challenging to manage.

Skin involvement occurs in 0.7-9% of patients with all types of cancers [1-3] but breast cancer is the most likely solid organ cancer to metastasise to the skin. Patients with recurrences limited to subcutaneous layers has a lower chance of developing distant metastases, a better overall survival rate and a greater likelihood of remaining disease free once the recurrence was treated than those patients with cutaneous chest wall recurrence [4].

Treatment is often limited to palliative control of symptoms. Further surgical intervention that may be possible includes wide local excision of cutaneous metastasis with or without myocutaneous flaps and in extreme cases chest wall, sternal and parasternal resections [5-7]. However these are extensive operations which in some cases are not well tolerated by patients. Radiotherapy cannot be used repeatedly as there are definite limits to the amount of radiation that normal tissues will tolerate and previous irradiated tissue may not be amenable to further radiation or limited to low doses only. While chemotherapy is the main modality of treatment for patients with metastatic breast cancer, many women receive chemotherapy for only small gains in survival [8] and cutaneous disease is not very responsive to chemotherapeutic agents therefore a careful balance is needed between the potential benefits of chemotherapy and its toxic side effects. Therefore methods of treatment which adequately treat recurrences with minimum toxic side effects are needed to improve the conventional treatment options.

Electrochemotherapy

Electrochemotherapy is a non-thermal tumour ablation modality which is based on the local delivery of electrical pulses that increases the permeability of the cell membrane to non-permeant or low permeant cancer drugs. It is based on the concept of electroporation which allows low permeant drugs like bleomycin and cisplatin to enter the cell, thus enhancing their cytotoxicity by orders of magnitude. [9,10].

High-intensity electric field applications with short durations can allow intracellular manipulation and could be used to induce cancer cell apoptosis [11,12] in themselves.

How does it work?

Electroporation (EP) facilitates drug transport of molecules through cell membranes that are poorly or non-permeant)[13] (Figure 1). Indeed, most clinical data has been restricted to bleomycin, which has its action potentiated between 1000 and 5000 fold and cisplatin, which has its action potentiated from 10 to 80 fold by electroporation of cells [13,14]. The improved cytotoxicity of these agents is thought to be facilitated by a secondary consequence of electrochemotherapy-vasoconstriction with endothelial disruption. Firstly a short-lived episode when the electric pulses are delivered using cliniporator™ attached to appropriate electrodesafter administration of chemotherapeutic agent (Figure 2). This results in a 'vascular lock' around the tumour cells which prevents wash-out of the cytotoxic agent and further concentrates the cytotoxic agents in the tumour cells. Secondly the disruption of the endothelial cytoskeleton and intracellular junctions reported *in vitro* studies results in a change in the configuration of the surface of the endothelium. This leads to an impaired barrier function and interstitial oedema resulting in decreased intravascular pressure and compromised blood flow. Repair of the endothelium is slow and a reduction in blood flow in feeding tumour vessels causes severe hypoxia to the tumour after treatment with ECT.

Clinical trials on electrochemotherapy have been performed most frequently in patients with advanced metastatic cancer in whom the possibility of standard treatment has been exhausted [15].

Following on from a number of small studies on electrochemotherapy in the treatment of cutaneous metastases which showed promising results, in 2006, The European Standard Operating Procedures of Electrochemotherapy (ESOPE) study funded by the European Union, five countries evaluated and confirmed the efficacy and safety of electrochemotherapy [16].

This two years long prospective non-randomised study enrolled patients with progressive cutaneous and subcutaneous metastases of any histologically proven cancer. They treated 61 patients using electrical pulses with bleomycin or cisplatin chemotherapy [16,17]. They found an objective response rate of 85% achieved on the electrochemotherapy treated nodules, regardless of tumour histology.

They demonstrated electrochemotherapy is effective both in the irradiated and non-irradiated skin, as 85 of the 171 nodules treated in the study were in previously irradiated skin. One of the most promising aspects of electrochemotherapy is its unique ability to selectively kill tumour cells without harming normal surrounding tissue [18]. Furthermore, it can be used on elderly patients where surgery is less of an option [16].

The ESOPE study standardised the operating procedures for electrochemotherapy and confirmed that electrochemotherapy is an easy, effective and safe approach for cutaneous and subcutaneous metastases. Side-effects were minor and acceptable, as reported by the patients [15]. Indeed, 93% of patients indicated that they would be willing to accept the treatment next time if indicated [15].

This has been shown to be a successful, well-tolerated approach to managing cutaneous manifestations of breast cancer and loco-regional recurrence. A number of studies have shown ECT can induce partial or complete response of nodules to the therapy, preventing nodules from lesions which are associated with bleeding or skin ulceration may be

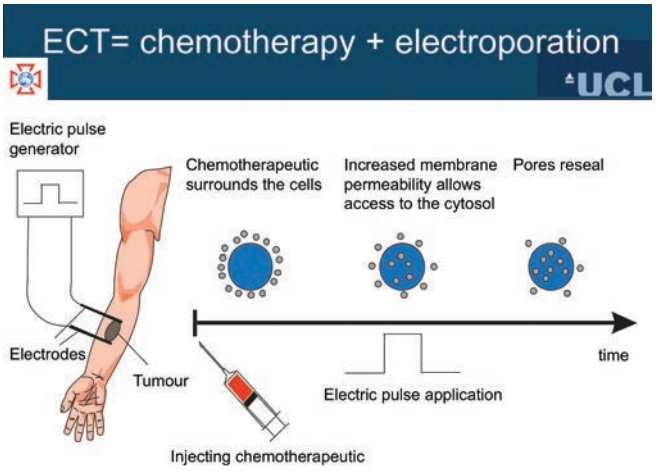

Figure 1: Mechanism of action of electrochemotherpy

Figure 2: Electrochemotherapy using cliniporator™ in progress in a breast cancer patient with cutaneous metastases of chest wall.

benefit from this treatment which would otherwise be un-resectable and refractory to other treatments. A number of authors have demonstrated that ECT is effective in causing immediate cessation of bleeding and reduction in ulceration.

It is an easy, highly effective and safe treatment approach for cutaneous and subcutaneous tumour nodules and is quick to perform (median time of treatment 25 minutes in the ESOPE study). In patient stay is usually two to three days and is variable according to degree of post–operative discomfort/pain requiring in-patient treatment. Furthermore, the procedure can be performed under local anaesthetic for small areas increasing the treatment modalities of patients with co-morbidities which prohibit the use of general anaesthesia.

Currently the application of Electrochemotherapy to patients with breast cancer is largely limited to those patients who have advanced or recurrent disease. Furthermore, studies so far do not seem to affect the overall natural history of breast cancer [19]. Electrochemotherapy is not recommended for patients with symptomatic or rapidly progressive non-skin metastases, due to reduced life expectancy and ethical implications [19]. Contra-indications for electrochemotherapy include the presence of a pacemaker precluding treatment on the anterior chest wall, and sensitivity to bleomycin or a history of pulmonary fibrosis as bleomycin can potentially cause acute or chronic pulmonary fibrosis.

Discussion

Electrochemotherapy is an emerging technology which provides an effective alternative treatment for breast cancer patients with chest wall metastases who have previously received adjuvant radiotherapy, and is an option when all other therapies have failed. However it may have beneficial effects to patients at an earlier stage of the disease. In order to explore this further a multi-centre, clinical study is needed to investigate the efficacy during early and late intervention. The experience gained by individual centres which have established electrochemotherapy as a part of their standard of care for breast cancer management can help to improve the application of the technology as a whole. The challenge ahead is to provide a platform to facilitate sharing of this experience with centres who wish to embark on the use of electrochemotherapy so that a consensus approach regarding patient selection, in-patient management and post-operative care can be agreed and adopted by centres using this technology. NICE will be issuing their guidance on this technology imminently, let's watch the space... ■

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