Electrochemotherapy in Cancer Treatment

RCT summary for professionals

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1. Abstract

Electrochemotherapy (ECT) is a local tumor treatment based on the induction of cell membrane electroporation combined with the local or systemic administration of low dose cytotoxic drugs. The technique uses pulsed, high-intensity electric fields to temporarily increase the permeability of the cell membrane, through which the chemotherapeutic agent can easily diffuse inside cells before the membrane recovers its impermeability. The two most commonly used drugs are bleomycin and cisplatin which do not freely cross the intact cell membrane and directly affect the nuclear DNA structure, adversely interfering with mitosis leading to cancer cell death. ECT in general today can be considered as a palliative option for cancers for which standard treatments (e.g. radiotherapy, chemotherapy, and surgery) have failed or proved to be insufficient. The tumors most frequently treated with ECT are skin melanoma, as well as breast cancer chest wall recurrence, basal and squamous cell carcinoma, Kaposi sarcoma and head and neck cancer. Currently the technology is being developed for treatment of larger, deep-seated tumors such as liver or bone metastases. ECT is available as a treatment mainly in clinics in Europe but clinical trials are underway in Australia and the USA. This review is intended to summarize the recent clinical outcome as well as to achieve a broader awareness of this therapy.

Synonyms: electrochemotherapy, electroporation therapy

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2. What is it?

2.1 Introduction

The development of new anticancer drugs has not been very successful since it has been found that the administration of drugs alone does not result in sufficiently high intratumoral concentration concomitant to reduced systemic toxicity (Besić, 2007). In the attempt to improve the anticancer therapy, various delivery systems, such as liposomes or nanoparticles to name but a few, have been introduced to minimize the systemic drug exposure and bring the anticancer drugs to the site of interest. Special strategies, such as receptor-mediated drug delivery, have also been adopted for enhancing the tumor delivery of anticancer agents. Although, some of these methods have resulted in successful enhancement of the intratumoral drug concentration and marked anticancer activities, they have not shown any appreciable progress in anticancer therapies and only very few products have actually reached the market. In order to introduce new mechanisms of drug delivery and to develop suitable carrier systems for anticancer agents, new strategies based on the application of physical methods and techniques have been established in the last two decades. Electrochemotherapy, the combination of reversible electroporation with the administration of otherwise low-permeant cytotoxic drugs, is an example of one of these developments.

Reversible electroporation of tissue has been used in conjunction with membrane impermeant anticancer drugs for almost twenty years as a form of cancer therapy known as electrochemotherapy (ECT). Stampfli was probably the first to mention the reversible breakdown of cell membranes in response to external electric fields (Stampfli, 1958). A few years later Coster observed the phenomenon of a “punch through” of the cell membrane by an electric field (Coster, 1965). Discussions on the increase in permeability of the plasma membrane of a cell due to the formation of pores, an effect subsequently named “electroporation” by Neumann and Rosenheck, appeared in 1972. These scientists demonstrated that exponentially decaying electric pulses between 18 and 24 kV/cm in amplitude and a field decay time of 150 microseconds induced a reversible permeabilization on medullar bovine cell granules (Neumann and Rosenheck, 1972). Kinosita and Tsong also suggested that this transient permeation is due to formation of pores with a diameter in the range of angstroms (Kinosita and Tsong, 1977). Electroporation then became a popular method in the laboratory to increase the bacterial or mammalian uptake of drugs, dyes, or DNA in culture.

In 1987, Okino and Mohri showed for the first time that high-voltage electrical impulses with concomitant application of an anticancer agent (bleomycin) had a strong inhibitory effect against in vivo growing solid tumor (Okino and Mohri, 1987). Similar preclinical investigations in the late 1980s (Orlowski et al. 1988) were followed by the first clinical trials demonstrating its effectiveness over bleomycin alone for the treatment of cutaneous metastases of head and neck carcinoma patients (Mir et al. 1991; Belehradek et al. 1993). These publications encouraged other investigators to expand the principles of this technique to other tumor types including basal cell carcinoma, Kaposi sarcoma, and melanoma metastases. In 1998, Sersa and coworkers introduced cisplatin as a therapeutic option (Sersa et al., 1998; 2000a). The main issue with most of the early studies was the utilization of a
variety of treatment protocols with different pulse parameters and pulse generators in combination with different electrode types and drug administration routes. But in 2006 the results of a pivotal prospective non-randomized multicenter ESOPE study (Marty et al., 2006) were published, providing recommendations for a standardized protocol for the procedure (Mir et al., 2006). Since then ECT has advanced considerably in terms of the systems used and cancers demonstrated to be suitable for treatment. The physical nature of reversible electroporation allows the technique to be applied to any cancer tissue. Based on a high number of preclinical and clinical studies this procedure as we will see has been established as a simple, safe and effective tumor treatment. The procedure can be performed as a single treatment of localized disease as well as a repeated palliative treatment of cutaneous metastases regardless of the tumor type. Its development has reached clinical application and is an example of successful translational medicine. There are more than 95 institutions almost all in Europe that continue to investigate and offer ECT as a palliative treatment for a variety of unresectable tumors.

2.2 Principles of electrochemotherapy

Electrochemotherapy (ECT) consists of the administration of a non-permeant (bleomycin) or poorly permeant (for example, cisplatin) drug with highly intrinsic cytotoxicity, followed by the application of short and intense electric pulses to the tumor. This temporarily results in increased cell membrane permeability, enhancing the uptake of these chemotherapeutic agents. After the electric field is discontinued, the pores close within minutes with the drug molecules trapped inside the target cells and without significant damage to the exposed cells (Mir et al, 1988; Giardino et al 2006). Two conditions are required for a high efficiency: a sufficient concentration of the drug in the tumor, and coverage of the whole tumor by an electric field above the threshold value for electroporation (Miklavcic et al., 2006; Mir, 2006). The types of drugs, the basic mechanism of reversible electroporation and equipment will be briefly discussed in the following sections.

2.2.1 Types of drugs

Two types of anticancer drugs are appropriate for ECT: non-permeant drugs with high intracellular cytotoxicity (Poddevin et al, 1991; Gothelf et al., 2003; Silve and Mir, 2012) and low permeant drugs with a well-known local antitumoral efficiency (Orlowski et al., 1988). Bleomycin and cisplatin have proven to be the most suitable candidates for the combined use with electroporation based on their chemical properties and molecular intracellular targets (Orlowski et al., 1988), with bleomycin being the most popular. Bleomycin is a non-permeant hydrophilic drug and normally almost no bleomycin molecules enter the intact cells (Pron et al., 1993; 1999). The high cytotoxicity of ECT with bleomycin can be explained by the fact that only several hundred internalized molecules of bleomycin are needed to kill a cell (Poddevin et al., 1991; Tounekti et al., 1993; 2001). After the electric pulses have generated changes in the cell membrane, bleomycin can cross the membrane freely, and easily reach the nucleus in less than 30 s. The drug then generates single- and double-stranded DNA breaks (Tounekti et al., 2001). The presence of these unrepaird strand breaks is not harmful for quiescent cells but it impairs the mitosis of dividing cells. Therefore, at the low doses of bleomycin used in ECT, this mitotic death mechanism affects dividing tumor
cells and spares quiescent normal cells. Among the low-permeant drugs, cisplatin has been the most extensively studied thus far in the clinics (Sersa et al., 2000a). In vitro studies demonstrated that toxicity of these agents is increased by electroporation more than 1000-fold for bleomycin and about 100-fold for cisplatin (Orlowski et al., 1988; Sersa et al., 1995). According to the findings of the ESOPE trial (Marty et al., 2006) administration of bleomycin proved to be effective in a systemic or intratumoral route, whereas cisplatin’s route of administration has to be intratumoral. In intravenous delivery, bleomycin enters the interstitial fluids of the tumor and subsequently the cells, provoking mitotic cell death as described above. In intratumoral administration of cisplatin, there is an increased local concentration of the drug that, in combination with its uptake by the cells and its toxicity after the application of the electric pulses, causes apoptosis of the cells exposed to the electric field (Mir, 2006). Systemic injection is suitable for the treatment of several nodules simultaneously or of large nodules (Mir et al., 2006). The effectiveness of ECT depends on the effective distribution of these cytotoxic drugs in the tumor and the permeabilization of the vast majority of the tumor cells. Other drugs have been tested but none has proven more efficient than bleomycin and cisplatin up to now.

2.2.2 Reversible electroporation

Under physiological conditions, the cell plasma membrane is subjected to a transmembrane electric potential difference (voltage) caused by a system of ion pumps and channels in the membrane. This voltage, termed the resting transmembrane voltage, is in the range of tens of millivolts and is present in every cell (Alberts et al., 2008). Exposure of a cell to an external electric field results in an additional component of the voltage across the membrane. This component, termed the induced transmembrane potential difference (also induced membrane voltage or induced transmembrane voltage), is superimposed onto the resting voltage and exists only as long as the external field is present. An external electric field also alters ionic currents and ion distributions in the extracellular space and activates a cascade of signaling pathways that upregulate transcription and translation levels (Hronik-Tupaj, 2012). The induced transmembrane voltage is proportional to the strength of the external electric field, and consequently exposures to sufficiently strong fields can lead to transmembrane voltages far exceeding their physiological range (Grosse and Schwan 1992; Kotnik et al. 1997; Kotnik and Miklavcic, 2000; Pucihar et al. 2006; Hu and Joshi, 2009). This can lead to structural rearrangements of lipids in the membrane bilayer due to large build-ups of oppositely charged ions on either side of the cell surface resulting in formation and stabilization of nano-size pores (Kotnik et al., 2010; Lee et al., 2012). This physical phenomenon was termed electroporation or electropermeabilization, because it was observed that molecules that do not normally pass the membrane gain intracellular access through diffusion after the cells were treated with electric fields (Neumann and Rosenheck, 1972; Mir et al., 1988; Schoenbach et al., 2006; Kotnik et al., 2010; Lee et al., 2012).

The mechanism through which the cell membrane is permeabilized is thought to be related to the formation of nano-scale defects or pores in the cell membrane, from which the term “poration” was derived. Multiple theoretical studies explored this phenomenon by molecular dynamics, electrical circuit modeling, and numerical simulations. Still, the mechanisms of electroporation itself and of electroporation-induced biological phenomena...
have not been fully understood (Kotnik et al., 2012). Two competitive theories exist. The most popular idea is the formation of hydrophilic pores in the membrane that last long enough to allow the passage of molecules (Neumann et al., 1982; Weaver and Chizmadzhev, 1996). However, these pores have never been observed experimentally. The second theory relies on the entrance of water molecules in the defects of the membranes created by the electric field (Pavlin et al., 2008; Kotnik et al., 2012). The membrane would then be more hydrated and more permeable to hydrophilic molecules such as bleomycin. This hypothesis is supported by molecular dynamics calculations (Tarek, 2005; Vernier et al., 2009).

There are several parameters to be taken into account when administering the electric component of ECT: electric field strength, pulse width (duration of the pulse), number of pulses, and pulse repetition frequency. Optimal parameters differ for different molecules and cell types. The intensity of the electrical treatments is described by the magnitude and duration of the applied electric field. If the field strength is too low, the breakdown transmembrane potential is not achieved; similarly, if the duration is too short, the membrane cannot be charged enough to reach the electroporation membrane potential (Schoenbach et al., 2006). Electric field strengths of a couple of hundreds V/cm or voltage over distance ratio (Corović et al., 2007) ranging from 1000 to 1300 V/cm have been used for ECT. Pulses are usually rectangular in shape. ECT has been performed with the pulse widths ranging from microseconds to milliseconds. The number of delivered pulses can range from one to eight pulses. Typically, multiple pulses are utilized during the ECT treatment. If the impulse duration is in the μs-ms range and the voltage-to-distance reaches 1-2 kV/cm, the resealing of the membrane occurs within minutes. The recovery of the membrane integrity after the electropulse has been shown in the reduction of the numbers of the colored cells by using the Lucifer Yellow or bleomycin cytotoxicity tests (Mir et al., 1988). Thus these electrical fields permeabilize the cell membrane temporarily after which the cells survive and then the process is known as “reversible electroporation”. In contrast to reversible electroporation used in ECT, the so-called irreversible electroporation (not the subject of this review) induces irrecoverable damage to the cell membrane without using cytotoxic drugs which ultimately leads to cell death and can be used in various applications, including tumor ablation (Rubinsky, 2007). In the reversible electroporation tumor treatments, cell death is caused by the drug, not by the pulses, resulting, at least in the case of the bleomycin administered intravenously, in a very selective destruction of the tumor cells only, sparing the normal non-dividing surrounding cells.

While the effects of electroporpermeabilization on the cell membrane have been well documented, it appears to also have a secondary effect on tumor vasculature. The application of ECT or even of electroporation alone in absence of the drug is known to induce a decrease in local blood flow (Sersa et al., 1999; 2008b; Gehl et al., 2002; Jarm et al., 2010). The local vascular-disrupting effect of ECT brought about by destruction of tumor vessels’ endothelial lining (Cemazar et al., 2001; Sersa et al., 2008b), is an important additional mechanism, which contributes to antitumor effectiveness of ECT. The killing of endothelial cells by ECT leads to permanent obstruction of tumor blood flow (i.e. a vascular lock) and consequently to ischemic death of all remaining cells supplied by the affected vessels. This finding mirrors the clinical observation that bleeding, ulcerated lesions cease to bleed following electroporpermeabilization (Gehl and Geersen, 2000; 2006; Snoj et al., 2009;
Jarm et al., 2010). Electroporation treatments would also promote an immune response (Mir et al., 1992; Sersa et al., 1997; Mir and Orlowski, 1999; Gerlini et al., 2012).

2.2.3 Equipment

Electrodes are used to directly connect the electrical source to the tissue under treatment. The electric field distribution, however, is determined by the geometry of the electrodes and tissue electric properties (i.e. conductivity). Regardless of the type of electrode the electric field is highest around and between the electrodes. It appears that plate electrodes are more suitable for use in superficial skin lesions, while needle electrodes are used for deeper seated lesions, such as exophytic and thick lesions (maximum depth 3 cm) (Marty et al., 2006). The electric pulses that may be applied to the tumors can be delivered by 4 different types of commercially available electrodes (IGEA). Type I electrodes consist of two parallel stainless-steel plate electrodes, used for superficial lesions and do not penetrate the skin. They are aimed at treating small and superficial skin metastases. A disadvantage of plate electrodes over the needle type is the potential skin damage that may be generated by the higher impedance/resistance of the skin, especially when treating larger affected areas (Möller et al., 2009). Type II electrodes are electrodes with parallel needle arrays and consist in 2 arrays of 4 needles separated by a 4-, 6- or 8-mm distance. They are used for the treatment of small nodules. Type III electrodes consist in hexagonal arrays of electrodes and are suitable for larger nodules (>1 cm). Type IV electrodes, called finger electrodes, allow the treatment of narrow body cavities not accessible by standard electrodes; they exhibit a good operator sensitivity and tactile feedback during the procedure (Möller et al., 2009). The needles are inserted directly into the tumor tissue and into the surrounding area, deeply to the subcutaneous level so that the entire tumor tissue can lie within the electric field generated. A detailed description of the different types of electrodes and their correct use is available in a paper by Mir and coworkers describing the standard operating procedures of ECT (Mir et al., 2006; Miklavcic et al., 2006).

The electric pulse generator applies a rapid series of brief, high-intensity, electrical pulses via a specific electrode into a solid tumor. Two pulse parameters have been evaluated - exponentially decaying pulses and square wave pulses. Of the two, square wave pulses are preferred as they permit independent control of the length and amplitude. Due to the numerous in vitro, in vivo and clinical studies (Marty et al., 2006; Mir et al., 2006), a standard has been defined for the electrical pulse delivery. It consists of 8 square-wave pulses of 100 μs with a voltage around 1000 V delivered at a repetition frequency of 1 Hz or 5 kHz (Mir et al 1991; Marty et al., 2006; Miklavcic et al., 2008; Sadadcharam et al., 2008).

A new generation of electric pulse generators has been developed that can produce electric fields for the treatment of larger treatment areas (Bertacchini et al., 2007; Möller et al., 2009; Miklavcic et al., 2010). A number of companies, notably IGEA (Cliniporator, IGEA, Carpi, Italy), Inovio (Medpulser, Inovio Biomedical Corporation, CA, USA), and OncoSec Medical System (OMS ElectroChemotherapy technology, CA, USA) have developed pulse generators and associated electrodes with approval for use in patients. The EndoVE is an endoscopic electroporation system EndoVE (MitaMed, Cork, Ireland) that connects to the Cliniporator. The Cliniporator is now approved and used in a large number of European
countries (Breton and Mir, 2011). New electroporator generators and new electrode devices will be soon available for the treatment of tumors located in more difficult-to-reach sites than the skin and subcutaneous tissue. The so called ‘finger electrode’ was developed according to a precise need of ECT users in order to allow treatments of tumors located in narrow body cavities not accessible to classical electrodes (Testori et al., 2012). The finger electrode has already been successfully tested in the treatment of tumors of the oral mucosa and head and neck region (Testori et al., 2012). Another approach that is in development is the use of endoluminal electrodes for the treatment of tumors in esophagus or in rectum (Soden et al., 2006). The translation of this technology into the human clinics is underway (Sersa et al., 2011). Also expandable electrodes for treatment of brain cancer are in research (Linnert and Gehl, 2009; Agerholm-Larsen et al., 2011; Mahmood and Gehl, 2011; Linnert et al., 2012) and commercially available (Sonion Medical).

2.3 Combinations of electrochemotherapy with other therapies

The combined application of ECT with other treatment modalities may provide an additional tool for cancer treatment since their combination is expected to exert an amplified effect regarding the efficient control of cancer. Preclinical studies have showed that ECT acts synergistically with radiotherapy, exerting a radiosensitizing effect on different types of tumors, which results in toxicity enhancement (Sersa et al., 2000b; Kranjc et al., 2003; 2009; Skarlatos et al., 2011; Raeisi et al., 2012). Also, ECT combined with photodynamic therapy (Lambreva and Berg, 2010) has been in research with the intention to enhance efficacy and achieve synergistic cell death. In addition, several studies suggest that the immune system is involved in the mechanisms of response to ECT treatment and that this could be exploited for systemic disease control. However, regression of untreated distant metastases has never been reported. Immunotherapy along with ECT would have the potential not only for local, but for distant treatment of tumors such as those of malignant melanoma, by stimulating a self-driven immune response to achieve systemic control of the disease. The involvement of the host immune system in the cure of tumors by ECT has primarily been shown in animal or in vitro studies. In studies on immunocompetent and immunodeficient nude mice it was demonstrated that the host immune response is crucial for effective ECT with bleomycin (Mir et al., 1991) and cisplatin (Sersa et al., 1997). The importance of the immune system was also demonstrated by other studies in which a combined use of ECT with various types of immunotherapy resulted in potentiation of ECT effectiveness (Mir et al., 1992; 1995; Heller et al., 2000). For example, interleukin-12 (IL-12) cytokine is a naturally occurring protein that is released by the body's immune cells to activate and increase the levels of circulating macrophages and cytotoxic T-cells to respond and eliminate not only foreign organisms infecting the host but also emerging cancerous cells. As a potential anti-cancer therapy, the introduction of pro-inflammatory cytokine proteins such as IL-2 into the body has produced some encouraging data (Andersen et al., 2003). Efficient systemic effects of ECT associated to IL-2 administration have been reported in mice (Mir et al., 1995; Orlowski et al., 1998) and in rabbits (Ramirez et al., 1998). In addition, a systemic antitumor response in animal models have also been found in ECT combined with the administration of Toll-like receptor agonists that activate the dendritic cells (Roux et al., 2008). Immunotherapy combined to ECT could broaden the therapeutic indications of ECT, by rendering it effective
also on distant unreachable or untreated lesions (Testori et al., 2012). So far, only a few data on the role of immunological response in ECT-treated patients have been reported.

2.4 Treatment planning, dosimetry and patient monitoring

ECT has been validated and its administration procedures standardized by means of two projects sponsored by the European Commission within the Fifth Framework Program. The first, a multidisciplinary project called Cliniporator, developed the technology to release electric pulses according to European Safety Standards. Within the second project, called ESOPE (European Standard Operating Procedures in Electrochemotherapy), a prospective multicenter clinical trial led by a group of researchers from Institute Gustave Roussy of Villejuif France, was conducted in collaboration with the Institute of Oncology Ljubljana, Ljubljana, Slovenia; University of Copenhagen at Herlev Hospital, Herlev, Denmark; and Cork Cancer Research Center Bio-Sciences Institute and Mercy University Hospital, National University of Ireland, Cork, Ireland (Marty et al., 2006). ESOPE defined the main indications, drug dosages and routes of administration, electrode configurations, etc. A standard operating protocol was developed for ECT of cutaneous and subcutaneous tumors that provides physicians with a set of appropriate electrodes and electric pulse parameters depending on tumor size and location (Mir et al., 2006). The ESOPE protocol is also valid for the ECT of deep-seated tumors. However, because of increased treatment complexity often linked to the use of needles placed independently in the tumor (Kos et al., 2010), an individualized treatment plan, similar to radiotherapy treatment plans, is necessary (Pavliha et al., 2012).

When planning ECT, doctors can choose between two possible treatment planning modes (Pavliha et al., 2012): following standard operating procedures with predefined geometry of electrodes based on models to predict electroporation, or a patient specific treatment planning. ECT based on predefined geometries was described for skin tumors (Marty et al., 2006) and brain tumors (Agerholm-Larsen et al., 2011; Mahmood and Gehl, 2011) and several clinical trials are registered and are ongoing. The first deep-seated tumors were treated and reported recently with ECT using long needle variable geometry electrodes, which demonstrated that patient-specific treatment planning is needed (Miklavcic et al., 2010; Edhemovic et al., 2011). Kos et al. (2010), Miklavcic et al. (2010), and Pavliha et al. (2012) have described in some detail the development of the procedure and treatment planning software that can provide medical practitioners with the information needed to effectively use electroporation in the clinical setting. The described protocols and algorithms have been intended specifically for ECT of deep-seated tumors; however, they are general enough to be useful for all electroporation based therapies. The treatment planning consists of several phases: image pre-processing, three-dimensional model generation, electrode placement, implementation of the mathematical model of electroporation, and optimization of the results to define the voltage applied which is dictated for each couple of electrodes by the number of electrodes and the electrodes positions.

The location of the tumor should be determined before treatment. Tumor location and size are determined by palpation with hand for the case of superficial tumors; however, in visceral tumors, location, size and shape are determined by means of computer tomography,
X-ray, nuclear magnetic resonance and/or ultrasound. A typical protocol for ECT of solid
tumors consists of an intratumoral injection of the chemotherapeutic drug or systemic
intravenous administration of bleomycin (the preferred route of administration), followed by
delivery of a sequence of (typically eight) square monopolar electric pulses to the tumor (Mir
et al., 1991). The ESOPE study concluded that intravenous or intratumoral bleomycin were
comparable when given to cutaneous and subcutaneous tumor metastases of volumes less
than 0.5 cm³ but intravenous route was significantly more efficient when tumors are above
this value (Marty et al., 2006). As we have seen, electroporation is responsible for a vascular
lock consisting in a reflex constriction of vessels after electric pulse delivery, producing a
temporary reduction in perfusion of tumor tissue (Gehl et al., 2002). This vascular lock effect
appears to last longer in tumor tissue compared with normal tissue. For this reason, the
cytotoxic drugs must be administered prior to electroporation (Testori et al., 2010). Electric
pulses are delivered at the time when the maximum extracellular concentration of the
chemotherapeutic drug is expected, so timing of electroporation is critical for successful ECT.
There is a relatively narrow time-window within which electroporation should be performed.
With intravenous administration, electric pulse delivery to the treated area needs to be
timed to the pharmacokinetic peak of the drug, which in humans is several minutes up to
half an hour or immediately within few minutes after the intratumoral injection of either
bleomycin or cisplatin, according to experience in previous clinical studies (Marty et al.,
2006). Not only is it critical to apply the right modality, it needs to be applied at the
appropriate dose for maximal benefit to be achieved. When bleomycin is given intravenous
the dose is 15,000 IU/m² of body surface area in a bolus lasting 30-45 seconds (Mir et al.,
1991; Marty et al., 2006; Möller et al., 2009). But when the intratumoral route is chosen,
both drugs are given in a dose calculation based on tumor burden (Mir et al., 2006).

Prior to each treatment session patients should have an electrocardiogram (ECG), blood
work for evaluation of renal function, coagulation and electrolyte values (Möller et al.,
2011). Cellular debris may be released from the tumor during electroporation and these may
interfere with the clearance of cytotoxic drugs by the kidney. Thus, when using intravenous
bleomycin, the serum creatinine should be maintained at less than 150 mol/L. Physiological
monitoring includes visual display of O₂ saturation, pulse rate, blood pressure, continuous
ECG tracing and respiratory parameters. Acetaminophen or an anti-histaminic medication
may be given to prevent the mild febrile reaction that may occur in the early post procedural
period when bleomycin is administered (Mir, 2006; Mir et al., 2006). The procedure can be
performed in the outpatient or ambulatory setting, under local anesthesia in association
with conscious sedation. General anesthesia may be preferred for larger tumors, or tumors
located in prior irradiated or fibrotic tissues where infiltration of local anesthetic may be
painful and less likely to diffuse and thus achieve adequate pain control as well as for those
located too close to vascular or bony structures. Postoperative response assessment is
required approximately 4-8 weeks after the treatment in order to determine effectiveness of
ECT by imaging or tumor histology. The treatment procedure has been extensively reviewed
elsewhere (Mir et al., 2006; Sersa et al., 2008a; Testori et al., 2010).
2.5 Advantages and limitations of electrochemotherapy

There are a number of potential benefits to the use of ECT. First and foremost, the drugs are used at doses much lower than cumulative doses usually used for systemic chemotherapy (Sadadcharam et al., 2008; Campana et al., 2009). The systemic dose of bleomycin, for instance, is one twentieth of that used in the majority of chemotherapeutic regimens. The effects are localized to the target area (only electropermeabilized cells are affected), therefore, no systemic side effects occur of the drug used (Testori et al., 2012). Moreover, in the case of the bleomycin administered intravenously, it has been shown that ECT will selectively eliminate the tumor cells because their division rate is much faster than the division rate of the normal cells surrounding the tumor. This high selectivity is one of the major advantages of ECT. Moreover, it is effective independently of histological types of tumors (Marty et al., 2006). Treated lesions heal without scar, due to the fact that the collagenic extracellular matrix and proteins are not denaturated by ECT, unlike other physical ablation technologies, thus allowing a faster healing of the wound (Mir, 2006; Marty et al., 2006; Campana et al., 2009). In some anatomical locations ECT could provide good and sometimes better cosmetic results than surgery (Sersa et al., 2009).

ECT is a feasible alternative in case of inoperable tumors, located in pre-irradiated areas and resistant to chemotherapy (Garbay et al., 2006; Whelan et al., 2006). The procedure is repeatable without loss of efficiency or induced drug resistance and its efficiency is not sensitive to previous surgery or radiotherapy (Breton and Mir, 2011). It achieves a high success rate in local tumor control with long-lasting responses after a single session (Testori et al., 2012). It proved to be a less invasive treatment option to eradicate early-stage tumoral lesions of the head and neck, strongly diminishing the elderly patient’s discomfort and risk derived from first-line surgery (Gargiulo et al., 2012). The absence of systemic side effects and the low impact on the immune system also make this treatment suitable for elderly people and patients with poor physical condition (Marty et al., 2006), even with repeated courses (Curatolo et al., 2012). ECT may also be used in the management of bleeding metastasis or as cytoreductive treatment before surgical resection (Sersa et al., 2012). Finally, this therapeutic approach can be applied in an outpatient regimen which may also provide economic benefits over conventional surgical and or radiation procedures through reduced operating theatre costs, hospital stays and post treatment interventions.

Several technical pitfalls exist for an optimal tumor electroporation. With the current available electrodes, ECT has limitations when treating deep-seated tumors (Sersa et al., 2008a). New electrodes development will soon overcome this issue. Tumors larger than 3 cm² appear to have lower response rates to ECT (Larkin et al. 2007; Quaglino et al., 2008; Campana et al., 2009) as compared to nodules smaller than 1 cm² (Möller et al., 2011). However, they can be retreated with no loss of the ECT efficacy (Campana, 2009). When tumor nodules are located in irradiated or fibrotic tissues the needle electrode penetration may be problematic with a suboptimal delivery of the electrical current or drugs (Campana et al., 2009).
3. Does it work?

3.1 Introduction

Electrochemotherapy (ECT) has received experimental and clinical support in recent years. In 2006, the multicenter European Standard Operating Procedures of Electrochemotherapy (ESOPE) project has defined and validated the standard operating procedures to safely and effectively treat patients with cutaneous and subcutaneous tumor nodules with ECT, thus providing the necessary guidelines for the use of ECT in clinical practice (Marty et al., 2006). In this 2-year long prospective, nonrandomized study, 62 patients were treated at four institutions. ECT was performed by using intravenous/intratumoral bleomycin or intratumoral cisplatin. An overall response of 84% (complete response 73%) was observed and no major side effects were found. Currently, several types of solid tumors are successfully treated by ECT in the clinic and the number of ECT users has increased during the last several years (Breton and Mir, 2011; Mali et al., 2012). This treatment modality has not been studied in randomized trials with other treatment techniques, such as ablative procedures or radiation therapy often because ECT was applied when no other procedure was known to be efficient in the patient’s oncological situation. ECT is now in development for treatment of deep-seated tumors, like in bones and internal organs, such as liver (Edhemovic et al., 2011). The technology is available with a newly developed electric pulse generator and long needle electrodes; however the procedures for the treatment are not standardized yet. ECT is now being used in more than 100 cancer centers over Europe (the majority in Italy and Germany) and it is estimated that in the year 2011 about 2000 patients have been treated by ECT (Sersa et al., 2012). There are four guidelines issued in Italy and one in Slovenia that quote ECT among the therapy to be used in melanoma treatment when surgery is not feasible. In addition, the National Institute for Clinical Excellence (NICE) is currently preparing documents on “Electrochemotherapy for cutaneous and subcutaneous cancer nodules”; “Electrochemotherapy for head and neck cancers including oral cancers”; and “Electrochemotherapy for the treatment of skin cancers (basal cell squamous cell carcinoma”. ECT has already been approved and reimbursed in several EU countries (Denmark, Germany, Greece, Italy, Poland, Portugal, Slovenia, UK).

This section highlights recent outcomes of ECT. The purpose is to summarize the clinical feasibility and effectiveness of ECT for each anatomical tumor location. Evidence for its efficacy comes from published research studies and clinical trials. Main focus is on phase 2 and 3 randomized controlled clinical trials if available. Thirteen clinical trials are registered in the ClinicalTrials.gov and seven in the ClinicalTrialsRegister.eu (access July 2012, intervention: electrochemotherapy, electroporation or electropermeabilization; drug: bleomycin or cisplatin). An electronic search of the Medline, Embase, Cochrane Library, and CancerLit databases was undertaken in June 2012. Two sets of keywords were used for the search strategy. One was for the ECT interventions; the other set was for each cancer type per anatomical location. No language restrictions were used. In vitro and animal studies, as well as abstracts have been omitted, including clinical studies published before 2005. Thus these selection criteria would benefit the rationale for rating the efficacy of ECT based on what is available in clinical practice today. Several tumor types not mentioned in the
following section such as inoperable colorectal cancer, brain metastases, and pancreatic cancer are currently in clinical trial.

3.2 Clinical applications of electrochemotherapy

3.2.1 Skin cancer

ECT provides effective local control of cutaneous and subcutaneous tumor 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 (Sersa, 2006). A European project (The European Standard Operating Procedures of Electrochemotherapy - ESOPE) was conducted with the aim of preparing standard operating procedures for ECT based on the experience of various European studies (Marty et al 2006). This multicenter study (level IV intervention) evaluated the effect of electroporation combined with either bleomycin or cisplatin administration in 62 patients with different cutaneous and subcutaneous malignancies, including melanoma. Bleomycin was administered either intravenously or intra-tumorally at a dose dependent on tumor size and cisplatin intra-tumorally only. Patients experienced a response rate of 85% (74% complete response rate) after only a single session regardless of tumor histology, type of drug administered or route of administration. At 150 days after treatment (median follow-up 133 days, range 60-380 days) local tumor control rate for ECT was 88% with bleomycin given intravenously, 73% with bleomycin given intra-tumorally and 75% with cisplatin given intra-tumorally. 57% of the cases treated in this study were melanomas.

3.2.1.1 Non-melanoma skin cancer

Bloom and Goldfarb (2005) determined the safety and efficacy of electroporation with bleomycin in patients with advanced squamous cell carcinoma (SCC) in a two open-label, multicenter, single-arm phase II study. Sixty-two patients with 86 SCC tumors of the head and neck were enrolled. Twenty-five patients were treated with bleomycin alone. Fifty-four patients were treated with electroporation and bleomycin therapy. In this study, bleomycin was injected intratumorally, whatever the size of the lesion. In the bleomycin alone group, one tumor showed a partial response and 36 tumors showed no response to treatment. In the bleomycin with electroporation group, 17 tumors showed complete response, 22 tumors showed partial response and 30 failed to achieve more than a 50% reduction in tumor size. Bleomycin with electroporation had a significantly greater number of patients showing a partial or complete response to the therapy when compared to bleomycin alone. Fifty-seven percent of SCC of the head and neck demonstrated a partial or complete response to ECT with the bleomycin injected intratumorally. In a previous section it was recalled that intratumoral bleomycin is not recommended for lesions larger than 0.5 cm³, which may explain the lower efficacy of this study.

Fantini and coworkers published the first case of palliative basal cell carcinoma (BCC) treated with ECT, with complete control of the disease, and concluded that ECT must be considered a therapeutical option in selected cases, due to ECT efficacy, good tolerance, simplicity of administration and minimal side effects, especially when patient condition or extension of the disease rules out traditional treatments (Fantini et al., 2008). Kis et al. (2012) consider
ECT also to be an additional tool in the therapeutic armamentarium for Gorlin-Goltz syndrome, and suggest using it as early as possible in selected patients to avoid disfiguring scarring. They have based this proposal on a recent clinical study in which three patients were treated for a Gorlin-Goltz syndrome characterized by numerous BSCs with ECT using intravenous bleomycin. Clinical response was obtained in 98 (99%) of the lesions, 86 (87%) of them showed complete response. In 2 tumors, regression was confirmed with histological examination. Long-term cosmetic results were excellent. Landström et al. (2010) evaluated the efficacy of ECT and intratumorally injected bleomycin in treating BCC and SCC of the head and neck in six patients. Orbital growth, facial nerve proximity, or proximity to cartilage of the external meatus complicated four of these tumors. The follow-up period was 24 months and included biopsies after 8 weeks. In four of the six patients, one treatment was enough to eradicate the tumor. In one patient, the tumor persisted even after a second treatment with ECT. One additional recurrence was recorded 6 months after the follow-up period. This study, however, was too small to allow any statistically valid conclusions. Curatolo et al. (2012) treated twenty-three patients with unresectable Kaposi Sarcoma (KS), not treatable by radiotherapy or intralesional vincristine therapy. A response to the first ECT session was obtained in all patients, with a complete response in 14 (60.9%) of 23 patients. A second ECT was performed in 5 (21.7%) and a third in 2, with a median interval between two sessions of 5.1 (range 2.5-25.5) months. Overall, a total of 15 patients (65%) experienced a CR. After a median follow-up of 1.5 years (range 2 months to 4.2 years), 16 patients maintained the response, 4 after repeated courses. Sustained local control of treated lesions was present in 20 of 23 patients. The overall survival rate was 74.4% at 2 years. In another prospective study by Latini et al. (2012) the long-term efficacy of bleomycin-based ECT on disease progression and viral activity in Kaposi's sarcoma-associated herpesvirus was evaluated. Eighteen patients affected by isolate or multiple cutaneous lesions, refractory to conventional treatments were enrolled in the study. Follow-up visits were performed after 4 weeks and every 6 months for up to 48 months. The results showed a significant clinical improvement in all patients after 4 weeks. A complete regression was observed in 12 patients after the first ECT, while four patients required a second treatment on the residual lesions after 4 weeks from the first intervention. The positive outcome persisted during the subsequent clinical control visits. Two patients, that showed rapidly evolving disease did not improve and relapsed despite a second round of ECT treatment. Effective treatment was associated with the reduction of viral load to undetectable levels. These data support the conduct of larger studies directed at validating the efficacy of ECT as a first-line therapy for KS.

3.2.1.2 Melanoma skin cancer

In recent years, the effectiveness of ECT treatment has been confirmed in several small series of patients with melanoma. In patients with unresectable recurrent or in-transit melanoma disease who are not candidates for standard surgical or medical treatment, ECT is now an important therapeutic option (Möller et al., 2011). These cases include those with unresectable disease due to the extensive number of nodules or lesions located in compromising anatomic areas, such as those around joints, nerves, distal leg and in previously operated fields. Encouraging results with long term remissions have been documented (Breton and Mir, 2011; Testori et al., 2012).
Gaudy and coworkers published a randomized study comparing the effect of electroporation on melanoma metastasis versus electroporation associated to intralesional administration of bleomycin (Gaudy et al., 2006). Patients included in the study presented at least 2 tumoral nodules in stage III and in transit metastasis or nodules in stage IV not responding to standard chemo- and radio-therapy. Fifty-four tumoral nodules from 12 patients were treated. Twelve weeks after the procedure complete response was observed for 11 out of 30 nodules (36%) treated with electroporation plus bleomycin against 8% (2 out of 24) treated with electroporation only. In two further studies, Quaglino et al. (2008) and Campana et al. (2009), similar response rates to the above mentioned ESOPE study (subchapter 3.1) were observed. Quaglino and coworkers studied the response rate of metastatic melanoma following ECT with intravenous bleomycin. The probability of local tumor control was identified as 74.5% at 24 months and of the nodules that achieved complete response, none relapsed. Additionally, this study identified that repeated treatment sessions increased tumor control, especially in nodules >2cm², i.e. if a partial response was achieved after the first treatment, there was an increased probability of complete response after the second treatment. Campana et al. (2009) study focused on both melanoma and non-melanoma metastases and as with Quaglino et al. (2008) study, demonstrated similarly local tumor control (96% at nine months). The results also concurred with the Quaglino et al. study in that there was increased tumor control after repeated treatment. Additionally, this study documented the significant improvement in both the bleeding and pain associated with the tumors and the patient’s quality of life. Snoj and coworkers also reported on effective treatment of melanoma bleeding metastasis, 3.5 cm in diameter, by ECT (Snoj et al., 2009). In this case, all standard treatment modalities were reported to be employed, but none of them provided a long-term result. Thus, amputation of the lower limb was considered. A single session of ECT with bleomycin, however, provided an immediate clinical benefit; the bleeding stopped and did not recur. In addition, a crust developed and a reduction in size was noticed. It was concluded that ECT should be considered both as an effective treatment in palliation of bleeding melanoma skin metastases and as an effective modality for limb-sparing treatment of refractory bleeding melanoma nodules.

More recently, Kis et al. (2011) compared the clinical effectiveness of ECT as an alternative palliative treatment option for unresectable metastatic lesions of malignant melanoma with reported outcomes. One hundred fifty-eight cutaneous and subcutaneous metastases of nine patients were treated with ECT. All treatments were performed under general anesthesia using intravenous bleomycin injection. Median follow-up was 195 days. Complete response rate was 23%, and partial response rate was 39%. No change was observed in 30% and progressive disease in 8% of cases. Their results provide further data for the growing body of evidence in recently published studies that ECT used for palliation has clinical benefit. Another phase II study was conducted in collaboration between a Danish and a British center (Matthiessen et al., 2011). Fifty-two patients with cutaneous metastases of any histology were included with bleomycin administered intratumorally or intravenously followed by application of electric pulses to the tumor site. Complete and partial response rate was 68% and 18%, respectively, for cutaneous metastases <3 cm and 8% and 23%, respectively, for cutaneous metastases >3 cm diameter. Treatment was well-tolerated by patients, including the elderly, and no serious adverse events were observed. ECT was also
offered to patients with superficially disseminated melanoma metastases unsuitable for resection and unresponsive to chemotherapy (Campana et al., 2012). Eighty-five patients were treated with up to six ECT cycles. One month after the first ECT, an objective response was observed in 80 patients (94%). After retreatment because of a partial response in 39 patients, a complete response was achieved in 19 patients. Among the 41 (48%) complete responders at first ECT, 19 patients received a second cycle because of new lesions after a median of 6 (range 2-14) months. After a median follow-up of 26 months, six patients experienced local recurrence with a 2-year local progression-free survival rate of 87%. An increasing number of electrode applications and ECT cycles were predictors of local control. Melanoma thickness and lower limb location of metastases were prognostic for survival. The most suitable candidates for ECT were patients with few and small metastases on the lower limb treated with multiple electrode applications and ECT cycles.

3.2.2 Chest wall breast cancer recurrence

Chest wall breast cancer recurrence after mastectomy is a disease difficult to treat. The importance of both local treatment and systemic treatment at every disease stage for breast cancer is highlighted by Punglia et al. (2007) who concluded that improved local control at five years resulted in a highly statistically significant improvement in both breast cancer survival and overall survival at 15 years. This highlights the role ECT has for this clinical indication. ECT provides safe, efficient and non-invasive locoregional treatment approach for chest wall breast cancer recurrence (Sersa et al., 2012; Matthiessen et al., 2012). Several clinical studies have demonstrated high efficacy and a good safety profile of ECT applied in single or multiple consecutive sessions, till clinical response was reached. ECT can be performed either with cisplatin injected intratumorally or with bleomycin given intravenously or intratumorally.

A number of studies included patients with breast cancer recurrence and skin metastases within their patient cohort. A study conducted by Campana et al. (2009) analyzed the outcome of bleomycin-based ECT in 52 patients with disease unsuitable for conventional treatments. Eleven patients of this cohort had chest wall recurrence from breast cancer carcinoma. Toxicity, local response, response duration, and the impact on quality of life were evaluated. A total of 174 tumor nodules were treated (mean, 15 per patient) in patients with chest wall recurrences. The outcome specifically for breast cancer patients are not reported but overall, after a median follow-up of 9 (range, 2-21) months, local tumor control was achieved in 50 (96%) of 52 patients, 31 with local complete response (CR) and 19 with partial response (PR). Through a nonvalidated eight-item questionnaire most patients reported a benefit in local disease-related complaints and in activity of daily living. In a palliative setting, ECT proved to be safe, effective in all tumors treated, and useful in preserving patients’ quality of life.

Muñoz and Ortega (2011) treated 63 patients with local curative intention and also with different histological tumor types. Of 25 breast cancer patients, 3 were locally advanced cases and 22 were local relapses, 13 were treated in Spain and 12 in Nicaragua. Ages ranged from 21 to 72 years and all were stage III–IV, with number of nodules ranging between 1 and 21, number of treatments performed between 1 and 3 and a minimal follow-up of 6 months.
Eleven out of 25 showed a complete response, 7 partial response and 7 died before the minimum follow-up period due to systemic spread of the disease.

The first systematic investigation of ECT for larger cutaneous recurrences of breast cancer was performed by Matthiessen et al. (2012). They conducted a phase II trial for patients with cutaneous recurrences where no further treatment options were available. Seventeen heavily pre-treated patients received bleomycin-based ECT. Twelve patients were evaluable (follow-up > 8 weeks). CT imaging showed four (33%) patients achieving over 50% tumor volume reduction, clinical examination showed one CR and one PR (OR 17%). Symptomatic relief included decreasing exudates, odor, and bleeding. This first phase II study may indicate that ECT is a treatment alternative for larger cutaneous recurrences of breast cancer.

### 3.2.3 Head and neck cancer

Several clinical studies regarding ECT of head and neck cancer have been reported. Tijink et al. (2006) applied bleomycin-based ECT on 2 patients with carcinomas of the oral cavity that no longer could be treated by surgery or radiotherapy, or for whom surgical treatment would be very extensive and thus declined by the patient. The main focus of the trial was to determine the safety, effectiveness, and burden of ECT for the patient. Local tumor control was reached in both patients after a follow-up of 8 and 12 months. Landström et al. (2011) assessed the local tumor control, survival, and effect on speech and eating after treatment of tongue cancer with ECT. Fifteen patients with primary T1 and T2 oral tongue cancer were treated with ECT and intratumorally administered bleomycin. Postoperative radiotherapy was performed when the tumor infiltration was 5 mm or more. The follow-up time was 24 months for the surviving patients and 20.4 months overall. No local recurrence was recorded in any patient during the follow-up. Of the 12 surviving patients, 2 patients had regional recurrence and 10 patients including the 5 patients treated with electroporation alone were tumor-free both locally and regionally at the last follow-up. The functional outcome for speech and eating were very good. In a study conducted by Skarlatos and coworkers (Skarlatos et al., 2011), ECT using bleomycin was successfully applied in combination with external beam radiation therapy in eight patients with very large tumors of the head and neck, which were either multi-treated or at an advanced stage. Mevio and colleagues (Mevio et al., 2012) evaluated the effectiveness of ECT (bleomycin) for the treatment of 15 patients affected by recurrent of extended primary head and neck cancer (13 squamous cell carcinoma, one basaloid carcinoma, one Merkel cell carcinoma) not suitable for standard therapeutic options. Electrical pulses were delivered to 33 lesions (3 primaries, 30 recurrences) less than 3 cm in diameter. Of the 31 lesions assessable for the study, 19 (61%) showed a complete response, 10 (32%) a partial response, 1 (3%) stable disease and 1 (3%) progression of the disease. The objective response 2 months after the procedure was 94%. After a follow-up of 2 to 20 months, 29% of the patients were alive and free of disease, 50% were alive with disease, 14% died for disease and 7% died for other causes. Gargiulo and coworkers (Gargiulo et al., 2012) evaluated the efficacy and safety of ECT using bleomycin in a large series of non-melanoma head and neck cancers. The primary objective was to evaluate the efficacy of ECT as a definitive and not just palliative treatment of cutaneous and mucosal head and neck cancer in nonsurgical patients, especially in those who are elderly or in a poor general condition. Twenty-five patients underwent ECT for the treatment of non-melanoma head and neck cancers. An objective response was achieved in 100% of all
treated patients at 6 weeks after the initial treatment. The complete response rate according to the WHO criteria was 72% (n=18) and the partial response rate was 28% (n=7). None of the lesions that achieved a complete response relapsed after a median follow-up period of 18 months. Partial responders showed stable disease for the duration of the follow-up. In accordance with the clinical results shown, the authors encourage further investigation to establish ECT’s use as first line treatment especially in basocellular carcinomas of the head and neck area and for squamouscellular carcinomas of the lip.

3.2.4 Liver cancer

Edhemovic et al. (2011) presented a single case of a treatment with ECT and intravenously administered bleomycin of a solitary metastasis in the liver of colorectal cancer within an ongoing clinical study. The procedure was performed intraoperatively by inserting long needle electrodes, two in the center of the tumor and four around the tumor into the normal tissue. Good antitumor effectiveness with complete tumor destruction was confirmed with histological analysis. The patient is disease-free 16 months after the procedure. The authors concluded that ECT proved to be a feasible technological approach for treatment of liver metastasis even in difficult-to-reach locations.

3.2.5 Cancer of the genital tract

A few case studies have been reported on using ECT and cancers of the genital tract. Curatolo et al. (2008) described the complete regression of a case of isolated penile Kaposi’s sarcoma after one course of ECT, underlining its efficacy and high tolerability in difficult anatomic sites. Also a 29-year-old female patient with recurrence of inoperable endometrial cancer was treated with intravaginal ECT and brachytherapy (Skarlatos et al., 2011). However, the patient had previously received external beam radiation therapy followed by brachytherapy. After 3 months, the disease remained stable. Subsequently, one application of ECT was performed in combination with brachytherapy to the surface area. ECT was performed with intravenous administration of bleomycin under general sedation. Complete response was histologically evident after two months, while the recurrence-free survival period was 9 months.

4. Is it safe?

4.1 Does electrochemotherapy have complications or side effects?

Many clinical studies have demonstrated that ECT using bleomycin or cisplatin has shown a low toxicity profile with very limited systemic side effects (Sadadcharam et al., 2008; Campana et al., 2009). The most common local side effects reported by the majority of patients are minimal local pain and transient redness of the skin (erythema) limited to the tumor and surrounding treated tissue (Testori et al., 2012). Most of the patients considered those symptoms tolerable as documented by the ESOPE study (Marty et al., 2006). In another study by Gaudy and coworkers, the most frequently reported adverse events were also localized pain (75% of patients) and erythema (17%), as well as muscle spasm (25%) and local tumor necrosis (42%) (Gaudy et al., 2006). However, this local tumor necrosis was
reported only in this study where intraliesional bleomycin application was used. The pain due to the insertion of the needles and the pulse delivery can be managed through local, locoregional, or general anesthesia as described in the ESOPE study (Mir et al., 2006). The erythematous reaction usually recedes within a few days (Quaglino et al., 2008). Delayed wound healing that may take several weeks or months to resolve, and epidermal erosions, and hematomas have been reported as rare events. Muscle contractions can be prevented by the injection of a muscle relaxant or by lifting the treated area away from the muscle for cutaneous lesions (Gehl, 2008). No arrhythmias or other pathological morphological changes in the ECG recordings during ECT have been found (Mali et al., 2008). Generally, the side effects of the electric pulse sequence such as edema, superficial epidermal erosion, or scars are scarce and heal rapidly. Symptoms related to ECT or hematologic toxicity have not been detected in any trial confirming the safety of this protocol (Breton and Mir, 2011). If extensive disease (more than 15 lesions) is present repeated sessions may be necessary. In aggressive disease, while undergoing ECT, new cutaneous nodules may emerge but palliative retreatment is worthwhile even though the systemic disease progresses rapidly (Testori et al., 2010).

4.2 Contraindications for using electrochemotherapy

The only contraindications of ECT are allergies to bleomycin and cisplatin, and for safety reasons ECT should not be used in patients with implanted electric devices such as pacemakers for lesions located close to the device and the heart (Breton and Mir, 2011). In addition, pulmonary, cardiac or liver impairment, epilepsy, active infection, brain metastases have been reported to be contraindications (Campana et al., 2012), as well as kidney failure (Testori et al., 2010; 2012). Also, patients who may carry a higher risk of bleeding such as those on anticoagulants or with an international normalized ratio (INR) >1.5 and platelets count of <70,000/mm³ should not be advised to choose for ECT (Möller et al., 2011).

5. Conclusions

The current direction of cancer treatments is toward a minimally and non-invasive strategy. In comparison to traditional surgery, minimally and non-invasive surgeries are positioned to transform the field of medicine with reduced surgical trauma, improved immune response and shorter hospital stays. We have presented in this review clinical evidence of electrochemotherapy (ECT) as an example of a minimally invasive treatment of cancer.

ECT is a drug delivery system appropriate for the treatment of cutaneous or subcutaneous malignant solid tumors in the setting of recurrent, progressive or inoperable disease refractory to the conventional anticancer therapies. It has proven its efficacy in many different tumor types, both in preclinical and clinical trials. In 2006, investigations of ECT in a multicenter study, called European Standard Operating Procedures for Electrochemotherapy (ESOPE), demonstrated that over 80% of cutaneous and subcutaneous metastatic nodules can be healed by ECT. Since this publication, clinical studies conducted with the classical protocol (as defined by ESOPE) have confirmed the efficiency of ECT on melanoma and breast cancer metastases as well as primary tumors of the skin, Kaposi sarcoma and head and neck cancer. ECT offers an excellent alternative for the treatment of these cancers.
owing to its highly selective treatment strategy, high probability of immediate relief, its outpatient basis and modest patient discomfort. It is now accepted in a number of countries as an inexpensive palliative local treatment. The technology of ECT, however, continues to evolve allowing for the treatment of primary or metastatic lesions in other organs or anatomic regions.

6. References

6.1 Scientific publications


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Whelan MC, Larkin JO, Collins CG, et al. Effective treatment of an extensive recurrent breast cancer which was refractory to multimodal therapy by multiple applications of Electrochemotherapy. EJC Suppl. 2006;4:32-4.

6.2 Books


6.3 Useful links

Bioelectrochemical Society: http://www.bioelectrochemical-soc.org
Electrochemotherapy on the Web: http://www.electrochemotherapy.org
European bioelectromagnetics association: http://www.ebea.org
http://www.cliniporator.com
http://www.electroporation.net
IGEA: http://www.igeamedical.com/oncology/electrochemotherapy-effective-treatment-cancer
International Network for Sharing Practice in Electrochemotherapy (INSPECT) database: (http://www.insp-ect.com)
MitaMed: http://www.mitamed.com
Sonion: http://medical.sonion.com
The Bioelectromagnetics society: http://www.bems.org
Video material: http://www.jove.com/video/1038/electrochemotherapy-of-tumours