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CLINICAL APPLICATIONS OF ELECTROCHEMOTHERAPY

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Abstract

Electroporation has several biomedical and industrial applications. The biomedical applications are in the field of drug or gene delivery. Electrochemotherapy utilizes electroporation for the increased delivery of cytotoxic drugs like bleomycin or cisplatin into tumors. The use of electrochemotherapy has spread throughout Europe for the treatment of cutaneous tumors or metastases. It is in the NICE guidelines and is becoming standard ablative technique in treatment of cancer. The technological advancements have also enabled the use of electrochemotherapy for the treatment of deep seated tumors, such as soft tissue or liver tumors. Clinical studies demonstrate good effectiveness on fibrosarcomas, colorectal liver metastases and hepatocellular carcinoma. However, electrochemotherapy is a local treatment that also induces moderate local immune response. This so called "*in situ* vaccination" induced by electrochemotherapy can be exploited in combined treatment with immune checkpoint inhibitors or electrogene therapy with immunostimulating effect. Therefore, gene electrotransfer of plasmid coding for interleukin 12 (IL-12), in combination with electrochemotherapy could result in transformation of electrochemotherapy from local into systemic treatment. This is also of our current interest, and we are undertaking steps to bring this idea from preclinical into clinical testing.

Key words: electroporation, gene electrotransfer, interleukin 12

Clinical importance of ablative techniques

Local ablative techniques are important for treatment of cancer. Some of the most recognized ones are radiofrequency and microwave ablation, cryotherapy and transarterial chemoembolization (TACE). Most of these approaches are thermal ablation techniques that are frequently used for palliation of symptoms in advanced cancers or as ablative techniques for treatment of liver and kidney tumors (Bailey et al.; Meloni et al. 2017; Ismail et al. 2018; Vogl and Gruber-Rouh 2019). Radiotherapy can also be considered as local ablative technique, since it has local effectiveness, but uses ionizing radiation for the cell kill in tumors (Wang and Haffty 2018).

The importance of these ablative techniques has recently been re-evaluated in the light of the new era of immunotherapy of cancer (Takaki et al. 2017; Mazmishvili et al. 2018; Wang and Haffty 2018). Emerging new drugs target the immune system blockade that is developed within the tumors. Tumor cells develop mechanisms to evade immune system control, by exposing ligands that block recognition from the immune system of the organism. These drugs, such as immune checkpoint inhibitors for CTLA-4 and PD-1 receptor or PDL-1 ligand (Ishida et al. 1992; Leach et al. 1996; Freeman et al. 2000), have brought vast improvements in treatment of cancer. About 40% of patients can nowadays be cured with these drugs (Wei et al. 2018; Darvin et al. 2018).

However, their effectiveness can be increased in combination with local ablative techniques (Calvet and Mir 2016; Yan et al. 2018). The reason is that local ablative techniques induce immunogenic cell death (Galluzzi et al. 2016), which stimulates the immune system even more, and synergize with immune checkpoint inhibitors (Dörrie 2017). Several studies nowadays explore these interactions and search for optimal treatment combinations that will push the boundaries in the curative treatment of cancer (McKenzie et al. 2016).

Another ablative technique is electrochemotherapy (Yarmush et al. 2014). It is a bimodal treatment using cytotoxic drugs bleomycin or cisplatin and electroporation as drug delivery system. This local treatment is gaining in importance and has been proven to have comparable antitumor effectiveness to other ablative techniques (Spratt et al. 2014). Its effectiveness is proven on a variety of skin, mucosal and deep seated tumors with complete response rate from 60-90%, depending on the tumor type (Sersa et al. 2008b). The technology is developing fast, and is nowadays practiced in 140 cancer centers

throughout the Europe (Miklavčič et al. 2014; Calvet and Mir 2016). Its use is also well recognized because of its known mechanisms of action, including the induction of the immunogenic cell death (Calvet et al. 2014; Ursic et al. 2018).

What is electrochemotherapy and its mechanisms of action?

Electrochemotherapy combines use of known chemotherapeutic drugs such as bleomycin or cisplatin with tissue electroporation. Electroporation is performed by application of electric pulses to the tumors, with high amplitude, which destabilize the cell membranes of tumor cells in the tissue, and increases the membrane for increased diffusion of drugs, which are otherwise not permeable or have hampered transport through the membrane (Sersa et al. 2008b; Yarmush et al. 2014). Therefore, electroporation is used as drug delivery system for bleomycin or cisplatin. Bleomycin cytotoxicity is increased for several 100 times and cisplatin for 50-70 times. The drugs can be injected intratumorally or intravenously. In both cases because of high cytotoxicity in tumors, facilitated by electroporation, low drug concentrations are needed, and therefore there are no systemic side effects related to drug administration (Gehl et al. 2018).

Besides the drug delivery to cells, other mechanisms of action are also involved in electrochemotherapy. The first are vascular effects of electroporation and electrochemotherapy. Electroporation induces vasoconstriction, which contributes to longer drug retention in the tumors. In addition, it enables drug diffusion into the endothelial cells, which consequently die as well. This leads to vascular disrupting effect of electrochemotherapy (Sersa et al. 2002; Sersa et al. 2008a). This phenomenon is important, because it prevents bleeding of the tumors due to the treatment with needle electrodes. More importantly, electrochemotherapy can be applied for the treatment of bleeding tumors, and can be applied in tissues with high vascularization, such as liver (Jarm et al. 2010; Zmuc et al. 2019).

The second is induction of the immune response. Nowadays it is known that after electrochemotherapy with cisplatin or bleomycin cells die with immunogenic cell death (Calvet et al. 2014; Ursic et al. 2018). This is a signal for the immune system to be activated, and therefore immune cells contribute to eradication of the remaining viable cells and induce complete responses of the treated tumors (Sersa et al. 1996; Sersa et al. 1997). This phenomenon is called *in situ* vaccination, and can be exploited by combination with drugs

that affect immune system of the organism (Sersa et al. 2015; Calvet and Mir 2016).

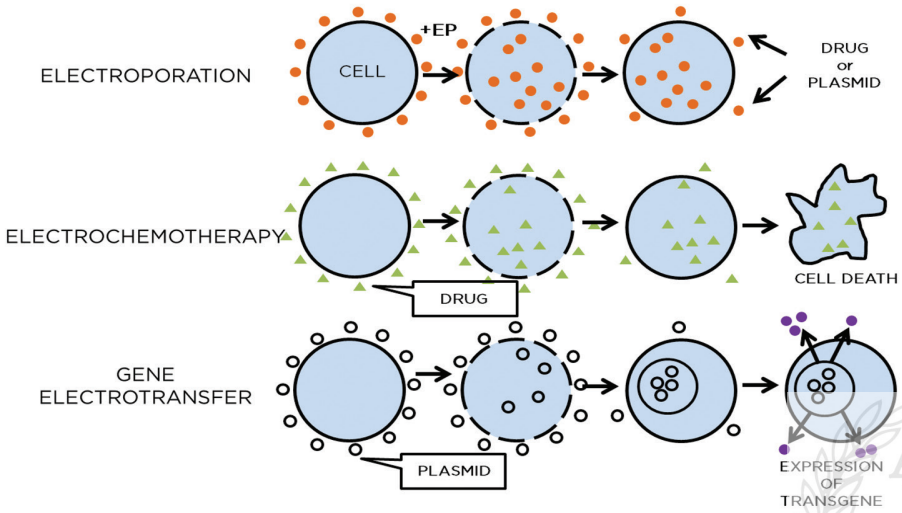

Figure 1. Biomedical application of electroporation. Electroporation: a platform technology for drug and gene delivery. Electrochemotherapy: delivery of chemotherapeutic drugs. Gene electrotransfer: delivery of a plasmid DNA.

What are the clinical applications in treatment of cutaneous tumors?

Currently electrochemotherapy is being used for the treatment of predominantly cutaneous tumors, either primary, recurrent or metastatic. The technology, *i.e.* electric pulse generator approved for clinical use, and pertinent electrodes, is spread throughout Europe in more than 140 cancer centers (Miklavčič et al. 2014; Calvet and Mir 2016). Initially, electrochemotherapy was used primarily with palliative intent, predominantly for melanoma cutaneous metastasis. Later on with publication of Standard Operating Procedures for electrochemotherapy, electrochemotherapy was used for treatment of cutaneous tumors of other histology, such as recurrent breast tumors, Kaposi sarcoma, and lately tumors in head and neck region, either basal cell carcinomas or squamous cell carcinomas (Mir et al. 2006; Gehl et al. 2018). In

the latter case, up to 100% response rate of the treated tumors was reported, whereas for the other tumor types the response rate varies from 50 – 80% (Bertino et al. 2016).

Electrochemotherapy is now in guidelines in many European countries. Most importantly it is in NICE guidelines, where it is also indicated for treatment of primary basal cell carcinomas, when the patients express the preference to be treated by electrochemotherapy (https://www.nice.org.uk). The most important organization that binds the biggest centers using electrochemotherapy is InspECT. The centers involved gather the data of their patients for the mutual, multicenter publications that strongly support the importance of the electrochemotherapy (Campana et al. 2016; Kunte et al. 2017; Rotunno et al. 2018; Matthiessen et al. 2018; Campana et al. 2019).

Lately, the Standard Operating Procedures have also been updated (Gehl et al. 2018). The purpose was to make them simpler and more user friendly. They advise the users and guide the physicians for the selection, and treatment of patients, as well as indicate the possible side effects and how to manage or evade them. This edited version is supposed to further contribute to the spread of the technology same as the first Standard Operating Procedures did (Mir et al. 2006).

Standard question that arises is: What is the efficacy of electrochemotherapy compared to other ablative techniques? This was nicely addressed in the meta-analysis published in 2013 where electrochemotherapy was evaluated to have comparable effectiveness to other ablative techniques (Spratt et al. 2014).

The technology development enabled treatment of deep seated tumors

The technological advancement of electrochemotherapy was in development of more powerful electric pulse generators, and designing of the electrodes for specific tissues and locations. This enabled the advancement of electrochemotherapy into the treatment of deep seated tumors. The first deep seated tumor treated by electrochemotherapy was deep seated metastasis of melanoma, where the treatment plan was also used (Miklavcic et al. 2010). Thereafter, colorectal liver metastases were treated with long needle electrodes that are inserted individually, also upon the prepared treatment plan (Edhemovic et al. 2011). The results of this phase I/II study were encouraging, with 80% response rate of the tumors. What is important is that the

tumors were predominantly located in locations that are difficult to treat, such as those in the vicinity of the major hepatic vessels. This brings the advantage of electrochemotherapy over radiofrequency ablation, because RFA is not effective in such locations due to heat sink effect (Djokic et al. 2018). The encouraging results of this first study have continued into extended phase II study, that is as effective as the first one, but the results have not been published yet.

Also treated were primary hepatocellular carcinomas in patients with impaired liver function, where surgery was not indicated (Djokic et al. 2018). These results are even better than in the study of colorectal metastases (Edhemovic et al. 2014). Complete response rate of even above 90% was observed (Djokic et al. 2018). The study is continuing in the phase II study.

Electrochemotherapy was also used in treatment of deep seated sarcoma tumors, bone metastases, and pancreatic tumors (Campana et al. 2019). These locations are still in the developmental phase, but are promising as well. The step forward would be to access these tumors percutaneously. Therefore, already first attempts were made on lyse hepatic trombi with electroporation (Probst et al. 2018), and also our radiologists have performed the first electrochemotherapy of hepatocellular carcinoma percutaneously (data unpublished).

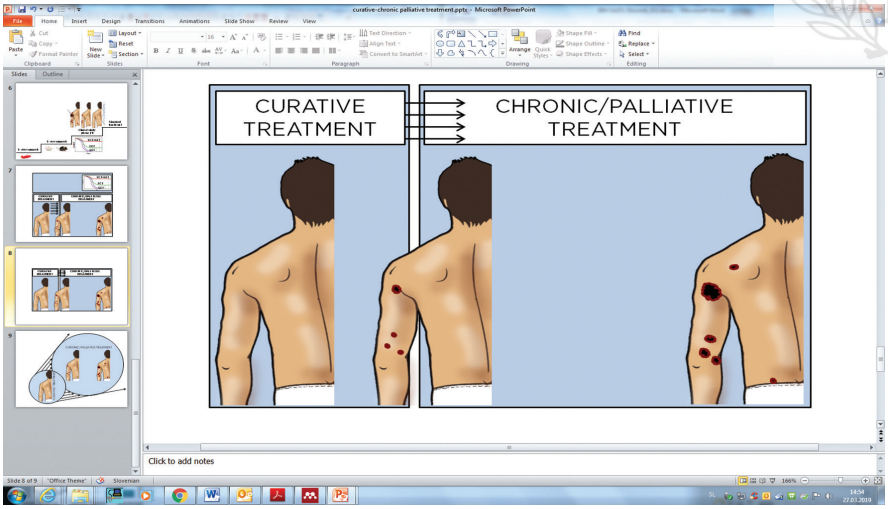

Figure 2. Pushing the boundaries of curative treatment. More patients with oligometastatic disease could benefit from local therapies.

What is the potential of combined electrochemotherapy with immunotherapy?

We are witnessing the revival of immunotherapy, with advent of new generation of drugs, the immune checkpoint inhibitors. These drugs deblock the immune response in the tumors. Namely tumors with time induce blockade of the immune system or resistance of cells to immune cells. Therefore, so called immune checkpoints can be targeted with monoclonal antibodies – immune checkpoint inhibitors (Iwai et al. 2017; Wei et al. 2018). The receptors and ligands are CTLA-4, PD-1 and PDL-1 (Ishida et al. 1992; Leach et al. 1996; Freeman et al. 2000). The drugs are currently used in treatment of melanoma and also some other tumors, with incredible efficacy, but only on 40% of the treated patients. Those 40% of patients can be cured (Darvin et al. 2018). However, there are indications that combining the immune checkpoint inhibitors with electrochemotherapy could increase the response rate over those 40% (Queirolo et al. 2014; Brizio et al. 2015; Calvet and Mir 2016; Heppt et al. 2016). As mentioned before, electrochemotherapy is seen as *in situ* vaccination (Sersa et al. 2015), due to the induction of immunogenic cell death in tumors (Calvet et al. 2014; Ursic et al. 2018), and this could contribute to the increased response rate of the patients (Wang et al. 2018).

The other option is to use immune stimulating approach. In this case in situ vaccination with electrochemotherapy is boosted by immunostimulation with cytokines, such as interleukin – 12. This approach can be also effective in making electrochemotherapy from local to systemic treatment. The model of such treatment combination and the underlying mechanism has been published already (Sersa et al. 2015; Calvet and Mir 2016).

Perspectives

Perspectives of electroporation based treatments is also gene electrotransfer (Cemazar et al. 2010; Yarmush et al. 2014). Plasmid DNA can be inserted into the cells by electroporation, therefore used for gene therapy. Gene therapy is becoming more and more interesting, especially with non-viral drug delivery systems, as gene electrotransfer is. There are already some clinical studies demonstrating feasibility and effectiveness of gene therapy using electroporation (Daud et al. 2008; Spanggaard et al. 2013). In line with this, gene therapy of plasmid coding for IL-12 would be effective in patients, as demonstrated in the study of Daud *et al* (Daud et al. 2008; Daud et al. 2014). Currently we are investigating and preparing a clinical trial where we would

combine electrochemotherapy with gene electrotransfer of plasmid coding for IL-12 into tumors in patients with cutaneous head and neck tumors. This would be a nice translational project into human oncology, which was already demonstrated feasible, safe and effective in veterinary oncology (Cemazar et al. 2017). In summary, biomedical applications of electroporation based technologies are promising and are currently under intensive investigation.

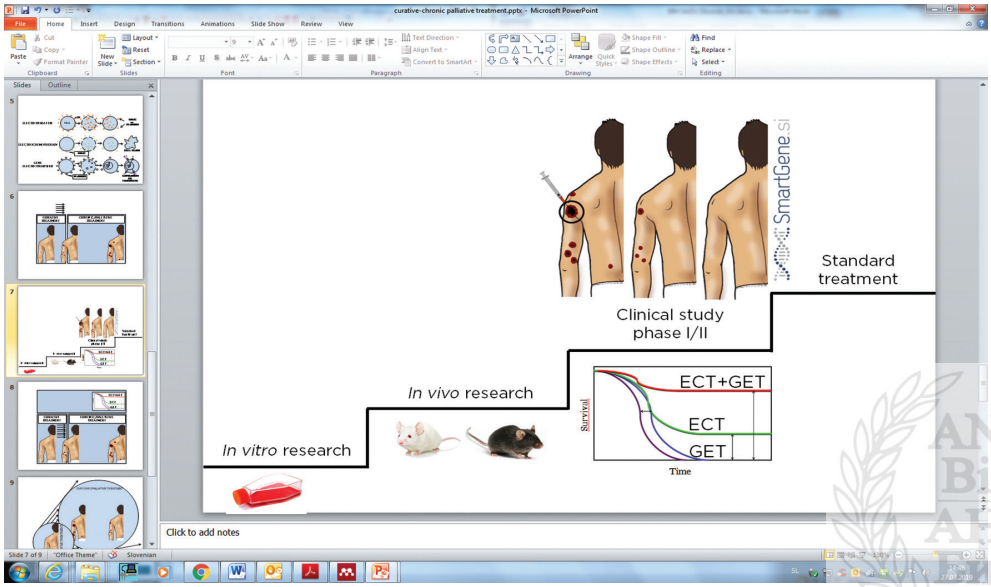

Figure 3. Translational research. The Department of experimental oncology advocate a translational approach, which encompasses both, preclinical and clinical research.

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KLINIČKE APLIKACIJE ELEKTROHEMOTERAPIJE

Sažetak

Elektroporacija ima nekoliko biomedicinskih i industrijskih primjena. Biomedicinske primjene mogu se naći u polju isporuke lijekova ili gena. U elektrohemoterapiji elektroporacija se koristi za povećanu isporuku citotoksičnih lijekova poput bleomicina ili cisplatina u tumore. Primjena elektrohemoterapije proširila se širom Evrope u liječenju kožnih tumora ili metastaza. Uvrštena je u NICE smjernice i postaje standardna ablativna tehnika u liječenju kancera. Tehnološki napredak također je omogućio upotrebu elektrohemoterapije za liječenje duboko usađenih tumora, poput tumora mekog tkiva ili jetre. Klinička ispitivanja pokazuju dobru efikasnost u liječenju fibrosarkoma, kolorektalnih metastaza na jetri i hepatocelularnog karcinoma. Međutim, elektrohemoterapija je lokalni tretman koji također potiče umjerene lokalizirane reakcije imunog sistema. Ova takozvana "*in situ* vakcinacija" izazvana elektrohemoterapijom može se koristiti u kombinovanom tretmanu s inhibitorima kontrolnih tačaka ili elektrogenskom terapijom uz imunostimulirajući efekt. Tako bi genski elektrotransfer plazmidnog koda za interleukin 12 (IL-12) u kombinaciji s elektrohemoterapijom, mogao rezultirati transformacijom elektrohemoterapije iz lokalnog u sistemsko liječenje. To je također naše sadašnje polje interesa i poduzimamo korake kako bismo ovu ideju iz pretkliničkih ispitivanja prenijeli na klinička ispitivanja.

Ključne riječi: elektroporacija, genski elektrotransfer, interleukin 12

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