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Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator™ by means of invasive or non-invasive electrodes

Lluis M. Mir[a,b,c,*], *Julie Gehl*[d], *Gregor Sersa*[e], *Christopher G. Collins*[f], *Jean-Rémi Garbay*[a], *Valérie Billard*[a], *Poul F. Geertsen*[d], *Z. Rudolf*[e], *Gerald C. O'Sullivan*[f], *Michel Marty*[a]

[a]*Institut Gustave-Roussy, 39 Rue Camille Desmoulins, F-94805 Villejuif Cedex, France*
[b]*CNRS UMR 8121, Institut Gustave-Roussy, F-94805 Villejuif Cedex, France*
[c]*Univ Paris-Sud, UMR 8121, France*
[d]*Department of Oncology, 54B1, University of Copenhagen at Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark*
[e]*Institute of Oncology Ljubljana, Zaloska 2, SI-1000 Ljubljana, Slovenia*
[f]*Cork Cancer Research Centre, Mercy Hospital, Greenville Place, Cork, Ireland*

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* *Corresponding author:* Tel.: + 33 1 42 11 47 92; fax: + 33 1 42 11 52 45.
E-mail address: luismir@igr.fr (L.M. Mir).
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1. Aim of the document

The aim of this document is to define the standard operating procedures (SOP) in order to safely and conveniently treat, by electrochemotherapy, patients with cutaneous and subcutaneous nodules. To this end this document provides the reader with the basis for understanding the mechanisms of the electrochemotherapy as well as its possibilities as antitumour treatment. It also has a decision chart to help the physician in choosing among the different treatment modalities reported in this SOP.

1.1. *Definition of ECT*

Electrochemotherapy is a new tumor ablation modality providing delivery into cell interiors of non-permeant drugs with intracellular targets. It is based on the local application of short and intense electric pulses that transiently permeabilize cells in tissues. To date, its main application has been the treatment of tumour nodules when the electric pulses are associated with non-permeant drugs having high intrinsic cytotoxicity. The most convenient drug is bleomycin, a currently used anticancer drug, but cytotoxicity of cisplatin is also increased in vivo by means of this original drug delivery approach.

It is important to note that the physico-chemical basis of this treatment allow to predict that it works on all the tumours types. Both the preclinical and clinical results published until now clearly support this assessment. It actually brings a new world of indications for the two drugs that until now have been proved efficient under this approach, the cisplatin and the bleomycin. The data already collected around the world have demonstrated the effectiveness of this technique which overcomes the ineffectiveness of classical chemotherapy and often allows avoidance of surgery, for example in previously irradiated areas. Moreover, it has repeatedly shown that hemorrhagic nodules stop bleeding immediately after the treatment, and the pain of painful lesions is also greatly reduced. The consequences of this treatment are simple, and taking into account the economic issues, the cost of this method is really low. This therapy should therefore be offered to the patients to improve their quality of life independently of life expectancy, to heal painful or bleeding lesions, as well as to improve the patient's cosmesis and associated social interactions.

Although ECT following the SOP here described can be performed with any electroporation system approved for clinical use and delivering 8 pulses of 100 μs at appropriate voltages, and with IT bleomycin doses different from those here recommended, we recommend that electrochemotherapy is performed with the newly developed Cliniporator™ machine that is CE certified for use on patients. This electric pulses generator has several advantages that make it a leading product on the market in this area. It generates square wave electric pulses with variable amplitude of electric pulses, and possesses two options for the frequency of the delivered electric pulses (1 or 5000 Hz). The device is computer controlled. There are several levels of the control: on the level of the machine manipulation as well as on the level of the electrical parameters that can be delivered. In addition it provides storage of the patient's characteristics as well as of the electrical parameters used for the treatment including traces of the voltage actually applied as well as the current delivered during the treatment. Moreover, the Cliniporator™ is the only device that offers the control of the pulses delivered on a screen, just after the delivery of the pulses. The operator can then receive a visual confirmation of the quality of the delivered pulses. In the case of an inadequate positioning of the electrodes, a trained user will detect the potential failure of the treatment and may repeat it immediately, without supplementary constraints for the patient (the electric pulses can be delivered again taking advantage of both the anaesthesia already operated and the dose of chemotherapeutic agent already injected). The Cliniporator™, CE marked, is produced by IGEA, an Italian spin-off company of the University of Modena that placed its experience at the disposal of the Cliniporator and ESOPE European consortia for the development, elaboration and distribution of Cliniporator™ to the medical community.

2. Principle of electrochemotherapy

Electrochemotherapy combines administration of non-permeant or poorly permeant chemotherapeutic drugs with application of electric pulses to the tumours in order to facilitate the drug delivery into the cells. Thus, enhanced drug delivery can substantially potentiate chemotherapeutic drug effectiveness, locally at the site of cell electropermeabilization by electric pulses, without affecting the tissues unexposed to electric pulses.

Based on numerous preclinical studies on electrochemotherapy using either bleomycin or cisplatin, the first clinical study on electrochemotherapy with bleomycin was performed in 1991 by Mir et al.[1] demonstrating good antitumour effectiveness on cutaneous metastases of head and neck carcinoma patients. After that initial study, several clinical studies on electrochemotherapy using bleomycin and cisplatin administered locally or systemically were initiated. Cutaneous metastases of different tumours were treated, such as head and neck squamous cell carcinoma, malignant melanoma, basal cell carcinoma, adenocarcinoma of the breast and salivary gland, hypernephroma, Kaposi sarcoma and transitional cell carcinoma of the bladder (reviewed in Gothelf et al.[2] and in Sersa et al.[3]). All together 1009 nodules in 247 cancer patients have been treated. Overall results of these studies show that electrochemotherapy is an effective treatment; objective responses were obtained in 48–100% of the treated nodules. Better response was obtained on smaller tumour nodules where the whole tumour mass could be adequately electroporated, than in bigger and thicker tumour nodules, where optimal tumour electroporation is more difficult to obtain. In some cases the treatment had to be repeated in consecutive sessions.

Electrochemotherapy is a new approach for the treatment of accessible tumour nodules, either cutaneous (this SOP) or

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