A web-application that extends functionality of medical device for tumor treatment by means of electrochemotherapy

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Electrochemotherapy (ECT) is a novel method for efficient tumor treatment in clinical environment. It combines local drug delivery and application of short high voltage pulses, which permeabilize the plasma membrane by electroporation. Drug can enter only the cells with permeabilzed membrane. Recently, medical device Cliniporator™ for controlled electroporation was developed. Here, we present a web-application that extends the functionality of this medical device. The aim of the application is to collect, store and to allow the analysis of every ECT application using this medical device. The application helps transferring data collected by device during the electroporation process to the central database, and enables filling of medical records through the web-forms. The application is based on technologies ASP, HTML, Flash, JavaScript, XML and others. The application main advantages are easy and rapid data access, scalability and independence of client computer operating system as well as easy application debugging and upgrading.

Key words: neoplasms-drug therapy; drug delivery systems; electroporation-instrumentation; internet

Introduction

In the cooperation with the European partners, the medical device called Cliniporator™ (IGEA s.r.l., Carpi, Italy) was developed, in the frame of the *Cliniporator* project (2000-03) funded by European Community. This device was designed for controlled *in vivo* cell permeabilization by electroporation. Electroporation is used to provide access to molecules distributed freely in the vascular and extracellular compartments that normally do not enter the intracellular compartments.[1,2,3] This technique is already used clinically to deliver cytotoxic molecules like bleomycin and cisplatin to solid tumors by *electrochemotherapy* (ECT).[4,5]

For a successful cell electroporation a voltage applied for a given electrode tissue geometry, pulse duration and number of pulses should always be in the range between reversible and irreversible threshold value. If the voltage applied exceeds the irreversible threshold value, a change in a cell membrane becomes permanent and destroys the cell. The most commonly very short (100 µs) high-voltage pulse or a sequence of such pulses are delivered. Pulses are generated in the high-voltage generator of Cliniporator™ and deliv-

ered through the needle or plate electrodes to the tissue. By measuring both current and voltage simultaneously the device is monitoring electrical property changes of tissue in real time.

Cliniporator™ is also the first medical device designed for *in vivo* DNA electrotransfer in clinical applications. The two key steps of DNA electrotransfer are the electroporation of the target cells and the electrophoresis of the DNA within the tissue. Therefore, the device delivers to the target cells a combination of short high-voltage pulse(s) that permeabilize the cells without substantial DNA transfer/transport, and a long low-voltage pulse(s) that do not cause permeabilization but facilitate DNA transfer into the cells. This non viral gene therapy method is called *electrogenetherapy* (EGT) and has many advantages with respect to viral methods.[6]

Indeed, the medical device Cliniporator™ is already used in clinical trials. They are performed in four approved medical centers in Europe, funded by European Community in a frame of ESOPE project (2003-2004). The aim of the project is to define Standard Operating Procedures (SOP) for electrochemotherapy and electrogenetherapy. Definition of the SOP can only be based on the wide study of ECT and EGT efficiency. Therefore, it is necessary to carefully follow and collect outcomes of ECT and EGT clinical trials.

For collection of data acquired in ECT clinical trials a standard paper forms (Clinical Report Forms - CRF) were prepared. The CRF consists of a number of subforms, of which extent depends on the number of treated tumors and number of sessions required to treat the tumor. The CRF include patient's general data, his/her medical history, tumor treatment data and response data. A tumor treatment can be repeated if necessary. The melanoma nodules can efficiently be treated by ECT, therefore patients with this type of tumors were included in the study. For every patient, medical personnel has to fill in 40

pages of forms on average. Since all forms are predefined and same for all patients, we decided to set up a unified database (*central database*) for collection of data from all four medical centers involved in the study. For submission of relatively high number of data into the central database we developed a web-application, which enables access to the central database and filling of forms from any computer connected to the World Wide Web.

Cliniporator™

Cliniporator™ is a medical device for electrochemotherapy and electrogenetherapy. It consists of two parts: a console (industrial PC compatible computer) for local collection of treatment data and user friendly interface; and an electroporator. Electroporator consists of a control unit, high voltage amplifier and low voltage amplifier. Control unit consists of a processor board, a measurement card for current and voltage measurement, a control card for driving voltage amplifiers and a control-relay card for switching between the electrodes.

A user controls the electroporator through graphical display and a keyboard of the console unit. He/she can enter relevant patient data, choose appropriate electrodes, and define pulse parameters such as number (e.g. 8 pulses), amplitude (up to 1000 V), duration (e.g. 100 μs), and repetition frequency (e.g. 1 Hz) of pulses. All users' presets are stored in a local database, which is integrated into the console. By pressing a foot switch, the user triggers pulse generation. Square-shaped pulses are delivered. During the pulse delivery, the control unit measures voltage and current through the load (a cell suspension or a tissue). After the pulse application voltage and current measurements are stored into the local database. User can use the local database for later analysis of performed treatments. Based on collected data we intend to

develop an algorithm, which will allow device to adjust pulse voltage according to the current and voltage measurements in the real time and thus prevent irreversible changes in the cell membranes.

Central database

The central database (Microsoft SQL Server) stores following data collected from all the medical centers involved in study:

- patient data (demography, medical history, physical examination,...etc.),
- treatment data (sessions, evaluation visits, follow-ups,...etc.),
- data submitted from local databases of Cliniporator™ medical devices,
- images of tumor nodules in a different phases of treatment.

A backup copy of central database is automatically generated once per week.

Each medical center has limited data access. Users from one medical center cannot read or modify data entered by other centers. Entered data are protected by username and password. Every medical center can have more authorized users, who all have access to the same data. Users can lock selected data, so they cannot be accidentally modified (it is like signing medical forms).

Web-application

Since medical centers that share data in the central database are spread all over Europe, we had to develop an application for user interaction with the database, which is easy to install, debug and upgrade. It also had to be very intuitive for using, so the users (a medical personnel) should not require any computer knowledge background or excessive training. It had to involve functionalities like: filling the clinical report forms (CRF), interactive human map for marking location of nod-

ules, uploading images to the central database, image gallery, uploading local databases to the central database, and review of already submitted data. In order to follow the progress of individual centers the application also involves statistical representation of the submitted data. An important prerequisite, common in research studies, was that the system has to be upgradeable.

A client-server application would be costly to maintain and upgrade, therefore such solution was not acceptable. Therefore, we developed a web-application (*called Cliniporator Web-Recorder*), which is in our opinion an optimal solution. Such solution does not need any installations on a client computer. Clients can access the central database through the web-application from any computer connected to the World Wide Web and installed internet browser (Internet Explorer, Netscape, Mozzila,...). The web-application is executing on a web-server. The application speed depends only on the web-server capabilities and the internet communication bandwidth while the client computer does not affect the application speed. By submitting username and password users can access all the application functionalities according to their level of authorization.

Cliniporator Web-Recorder maintenance and upgrade is performed exclusively on the web-server. This is the quickest and the most effective and inexpensive way for debugging and upgrading the system. During the application development users have a possibility to participate in testing, which is very important for timely detection of irregularities in the system.

Cliniporator Web-Recorder functionalities are:

- web-forms (digital clinical report file (CRF));
- interactive human map for marking location of tumor nodules;
- image upload;
- local database upload;

- basic statistics (statistical processing of the submitted data).

Web-forms (digital CRF) are form-like web pages (Figure 1). Through digital CRF users submit patient and treatment data to the central database. Digital CRF have the same form as the paper-based CRF. They are organized in the following sections: pre-study visit, sessions, adverse events, concomitant medications, follow-up and end of study. The particular section is divided into several pages. *Pre-study visit* consists of few pages where users enter patient's demography data, medical history (history of cancer, previous treatments and history of chronic non malignant diseases), vital signs, physical examinations, tumor lesions, laboratory results, inclusion criteria and exclusion criteria. Users can add any

number of *sessions* (most usually two sessions). For every session users have to mark treated nodules and fill several pages with the following data: the time of the begin and the end of the session, vital signs, physical examination, post procedure data (memory from the procedure and pain assessment), and, later, day 15 and day 30 evaluation visit data (response to the treatment and memory from the procedure). Users can create one or more *follow-up* sections and enter data like date of the visit and lesion measurements. In the *end of study* section users should enter the reason for study termination. According to the already submitted data, some form-like web pages are dynamically generated, (e.g. if a patient has more tumor nodules, each nodule requires few form-like web pages for its description).

Figure 1. A digital CRF page.

An important advantage of the digital CRF is an automatic data checking. The web-application warns a user if he/she mistypes or enters erroneous data. The other advantage is a simple navigation through numbered forms.

At the end of every section users have an opportunity to »digitally sign« the completed section. By signing a section the corresponding forms are »locked« and all further modifications are disabled.

The purpose of the **interactive human map** is a visual representation of the tumor locations. According to the patient's sex, appropriate body map is displayed. Users can switch between four views: front, rear, left and right. By simply clicking on the map, user can »add« a tumor, and then submit some principal data about the tumor (location, measurement lesion, date and method of examination) and corresponding images. During the sessions, users can select on the map which of the pre-registered tumors are treated. The interactive human map is shown on the Figure 2.

Image upload enables storing of tumor images into the central database. Images, captured by a digital camera, can be uploaded in the original size. A smaller image, suitable for displaying, as well as a thumbnail of the image, are dynamically generated and also stored in the database. Users can add a caption and a description to every image. Images can be added in every phase of the treatment (pre-study, sessions, follow-up,...). In the *image gallery* (Figure 3) users can review all the uploaded images of one patient, or only the pictures of a particular phase of the treatment. This is very useful for the visual observation of tumor changes.

Local database upload is also performed trough the internet browser. The user simply selects the local database file and fills in comments. The rest of the process is automatic: application saves uploaded file on the server, records some upload information (date and time, user id, name of the file,...), and then copy data from the uploaded file to the central database. Application takes care of a duplicate data and their overwriting - the newer data will overwrite the older ones. At the end of the upload process user is informed about the upload success. In the list of the uploaded data user can check all the data uploaded from his/her center.
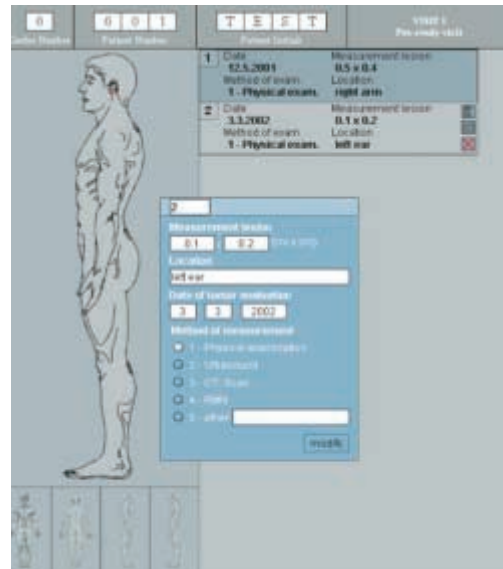

Figure 2. Interactive human map.

Figure 3. Image gallery: images are grouped by nodule and sorted by time.

Basic statistics, which allow the follow-up of the project progress, are dynamically generated from the data in the central database. Therefore, it offers information about the number of treated patients per center as well as number of ended therapies, number of tumor sessions and uploaded corresponding local databases, distributions of applications of different electrode types and different drugs. Every center has access to these statistics and can compare its activities with others. Some statistics (usually local statistics) can be dedicated to a particular center and therefore hidden from other users.

Conclusion

We have developed a web-application, *Cliniporator Web-Recorder*, for user interaction with the database of medical records collected during the testing period of medical device Cliniporator™. It also supports central collection of data stored in local databases of Cliniporator™ medical devices. This is important for fast detecting of possible device malfunctions and for following the single-use electrode stocks. The amount of data collected in the central database gives us an opportunity to perform a wide analysis of clinical trial results. The results of analysis will contribute to establish standard operating procedures (SOP) for electrochemotherapy and later for electrogenetherapy. These results will also help us in improving the Cliniporator™ medical device and determining algorithms for intelligent pulse delivery. A large collection of medical records can also be helpful to clinicians in choosing optimal treatment protocol for a particular tumor lesion. Our aim is to build a decision making system that will be able to suggest an optimal therapy for a particular tumor.

The advantage of the *Cliniporator Web-Recorder* is that the system can easily be upgraded without any users' disturbance. Due to the web-application and database centralization all system modifications are implemented locally on the server, while users are just informed about the improvements.

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