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Electrochemotherapy – A New Way for Enhancing Cancer Treatment

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Chemotherapy is a tool for killing fast proliferating cells, like most tumor cell lines, by means of therapeutic agents. Since the cell membrane is an efficient barrier for most chemical substances, many anti-cancer agents need to be applied in a high dose in order to reach a lethal level inside the cell. This in turn has implications for non-tumor cells yielding most of the known side effect of chemotherapy. There are perspectives for targeting drugs to the tumor in order to enhance the selectivity of the treatment, e.g. by means of magnetic field, liposomes or aptamers with high binding affinity to special cell lines.

Another way is the enhancement of the activity of anticancer agent at the site of a tumor using physical methods. First attempts to enhance chemotherapy by utilizing electric field range back to the end of the eighties of last century. Exploratory experiments by Okino and Mohri showed a drastic concentration increase of anticancer drugs in solid tumors. First clinical trials on head and neck tumors have been performed at 1990 by the group of Lluis Mir in France. Since this time a great development took place, involving many research groups, mostly in Europe and USA, resulting in efficient treatment procedures and commercialized equipment (e.g. Cliniporator, IGEA, Italy) for this purpose.

The most prominent anticancer agent used in Electrochemotherapy is Bleomycin, an almost obsolete drug which denatures DNA. However, for efficient action this drug should cross the cell membrane which is almost impossible for hydrophilic substances like Bleomycin. It was found, that a brief but intense electric field can enhance the transport of hydrophilic substance across the cell membrane by an effect called electroporation.

If a cell is attributed to an outer electric field, the highly resistive membrane will accumulate charges like a capacitor. This increases the trans-membrane voltage (usually termed membrane potential) from about -65 mV under resting condition up to about one volt. Charged plasma membranes are stable up to about 200 mV. Above this voltage water is forced into the membrane structure at preexisting defects (pre-pore) randomly probable due to molecular motion of the lipids. Increasing voltage increases the probability of creating a water structure which spans the entire lipid membrane, thereby creating a hydrophilic pathway with a dimension of about 1 nm. This is quite sufficient for the transport of hydrophilic substance like Bleomycin. Once the field ceases, self-organization forces a shrinking and finally resealing of these pores, thereby trapping the molecules transported into the cell during the presence of the electric field. Since the achievable concentration of water soluble anticancer agents inside the cell is by orders of magnitude higher than by passive diffusion through the low permeable cell membrane, any cell experiencing electroporation even in a low concentration of this drug will respond. This means, even if all cells of the body experience a low concentration, for instance of Bleomycin, only the cell attributed to intense electric field will respond. It is interesting to mention that the electric treatment with a field strength and duration as it is usually used in electrochemotherphy is not sufficient for killing cells since electroporation under mild conditions alone will be tolerated by most cells.

The procedure for electrochemotherapy involves commonly the drug injection at the site of the tumor. After some minutes, the tumor will be contacted by electrodes and the electric protocol with sufficient field strength for reaching electroporation condition within the tumor will be applied. First clinical trials were conducted at head and neck tumors because of the simple assessment. Surface electrodes have been the predominant electrode configuration in the early days. However, more sophisticated electrode systems for treating almost all tumors, e.g. caliper electrodes with adjustable electrode distance, needle electrodes for deep volume treatment or catheter electrodesappeared soon after.

Leading groups like L. Mir (France), J. Gehl (Denmark), G. Sersa, D. Miklavcic (Slovenia) or R. Heller (USA) demonstrated the efficiency of electrochemotherapy in clinical trials at humans but at animals as well. This approach is especially useful when tumors cannot be removed surgically like in case of bone metastasis.

Today, two anticancer agents, Bleomycin and Cis-Platin are mostly used for electrochemotherapy. Future work will focus on the development of new drugs, electrodes and diagnostic tools for more efficient guiding the electric field application and better feedback for the physician, especially if the site of the tumor is hidden and visual inspection possibilities are poor. Electrical characterization of the treated area for instance, gives information about the electrically induced changes on tissue level, even if they are invisible.

Since most of the development in Electrochemotherapy is of technical nature, many publications appeared in technical, often hard to access journals with only little attention by oncologists. A better attention from physicians was found for clinical trials published mostly in medical or biomedical journals or at dedicated conferences. For the success of new technologies a fast spread of the knowledge about it without the barrier of limited access to publications is essential.

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