Available online at www.sciencedirect.com

ScienceDirect

Ciência & Tecnologia dos Materiais 26 (2014) 126–130

Ciência & Tecnologia dos MATERIAIS

http://ees.elsevier.com/ctmat

Special Issue on Biomaterials

Electrotherapy, a recent mode for anticancer treatment

C.A.C. Sequeira*, D.S.P. Cardoso

Materials Electrochemistry Group, CeFEMA, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

Abstract

Cancer is a quite serious scientific and health problem, for which conventional or alternative therapies are used to solve these subjects. Among several methods, electrotherapy has been recently used by applying low and continuous electric current. In 1983, Nordenström reported in a systematic way for the first time, the main experiences and results using electrotherapy technologies with clinic effectiveness. In 1988, Pekar referred his experience about superficial tumours treatment using electrotherapy methods. Notwithstanding the great historic value of these experiences, this mode of treatment has not been so developed in occidental countries. Low cost combined with the high effectiveness of these processes lead China to a great development when compared to chemotherapy and radiotherapy. In this oriental country this technique is applied in more than 1200 hospitals, and reaches more than 9000 patients with serious cases. This therapy has been discussed by conventional doctors in several countries and recently has been observed a huge concern in this subject due to electrolysis phenomena. Based on published results it is intended to start improvements about electrotherapy. The aim of this first article is to evaluate the development status and its electrotherapeutical potentialities for cancer purpose.

Keywords: electrotherapy; cancer treatment; electrolysis anticancer mechanisms; mathematical modelling.

1. Introduction

Cancer can be defined as a cluster of cells with autonomy, called as tumour, which grows in an uncontrolled way and invades tissues near and far from those cells. Consequently, it causes severe damages to its organism [1]. Carcinogenesis is the process that explains the cancer creation starting from a normal cell [1-5].

This illness is the second cause to morbidity and mortality in the planet, corresponding to 8 millions of deaths (23% of global deaths in the world) occurred in 2007, according to World Health Organization statistics [6] and Union for International Cancer Control [7]. These international organisms predict that in 2020, the number of new cases and deaths should increase to 16 and 10 million, respectively.

Cancer, as referred before by Hippocrates in 5th century BC, became the main death cause in France after 2004 and has been estimated that will happen in the entire planet in this century.

These data show a serious epidemic of this disease as a social problem, due to the lack of knowledge and the need for different attitudes and therapeutic procedures in order to improve life quality and the guarantee of its survival. Thus, it is needed not only to beat the cancer as also to learn to live with it.

Conventional therapies for cancer are surgery, radiotherapy and chemotherapy [1], which are expensive, invasive, induce serious adverse effects on organism and they have not solved yet cancer cure completely, despite of many progresses. Actually, several developments for alternative therapeutic procedures have been done for this disease, which are mainly used as adjuvants of traditional ones. Among others can be mentioned: gene therapy [8] and anti-angiogenic procedures [9], anticancer vaccines [10], treatments using ascorbic acid megadoses [11], hyperthermia [12], electrochemotherapy [13], and

* Corresponding author.

E-mail address: cesarsequeira@tecnico.ulisboa.pt (C.A.C. Sequeira)

http://dx.doi.org/10.1016/j.ctmat.2015.03.005

electrotherapy or electrochemical therapy [14,15]. Electrotherapy involves the application of a continuous electric low intensity direct current, LIDC, using at least two electrodes which fall within the tumour and/or around it [14-17].

There are four modes of electrotherapy application [14-17]:

1. Anodic-cathodic treatment (anodes and cathodes are inserted into the tumour);
2. Field therapy (anodes and cathodes are inserted in the tissue at a distance between 8 and 10 mm of the tumour edges);
3. Anodic therapy (anodes are inserted inside the tumour and cathodes in the healthy surrounding tissue);
4. Cathodic therapy (cathodes are inserted inside the tumour and anodes in the healthy surrounding tissue).

In 1776, Eason proposed for the first time how electricity can have an important role for cancer treatment [18]. In the decade of 60-70, Schauble proposed the first scientific and technological fundamentals of electrotherapy in cancer [19]. In 1978, Nordenström applies for the first time electrotherapy in patients with lung cancer [20]. From these studies, there were a growing number of experimental researches (*in vitro, in vivo* and clinical) and theoretical (mathematical modelling) [16,21,22]. Xin [17] showed experience in benign and malign tumour treatments using LIDC in more than 20000 patients in China. These results were remarkable, but with insufficient advances in fundamental bases, mechanisms and standardization of therapeutic procedure.

Studies *in vitro* demonstrate that apoptosis can be induced when anodic treatment is applied and cell injury is produced when cathodic treatment is used [23,24].; modifications in cellular structures depends on therapy duration time and electrodes polarity [25]; cathode is submerged in alkaline solutions, while anode is immersed in acid medium [26]; apoptosis is initiated by the formation of reactive oxygen species after inducing LIDC [27].

Researches *in vivo* indicate several biochemical changes around anode and cathode [28]; in presence of necrosis in treated area [29]; cellular toxicity changes based in electrodes distance and its polarity [30]; increment of tumour destruction and decrease of organism damages when electrodes are inserted in the heart of tumour [31]; sensibility of various tumours after applying LIDC [32]; presence of apoptosis and necrosis around the anode and only necrosis around the cathode [33]. Similar results are reported in clinical researches about superficial and visceral malign tumours. [34,35]. *In vitro* and *in vivo* studies (animals and humans) show that electrotherapy is safe, effective, has low costs, traumatic situations are almost negligible, with minimum collateral effects and compatible with other therapeutic procedures. Moreover, this experimental therapy is employed when conventional methods fail or cannot be applied because of low physical state of the patient [34-36]. It has to be noticed that this technique is usually applied at once.

These researches discuss mainly the anticancer efficacy of LIDC and its secondary effects induced in organisms by cytotoxic action of this applied current, as well as finding the respective mechanisms for its anticancer action. Their results show that the anticancer effect of LIDC depends not only of electrode position but also of the applied voltage [37]. This method is well improved when combined with alternative therapeutic techniques such as chemotherapy [38] immunotherapy (e.g. TNF-α) [39], radiotherapy [40], hyperthermia [41], laser [42], ultrasound [43] and saline solutions [44]. The cell death observed in tumour treated with LIDC is caused by apoptosis and/or necrosis induced on that disease [45,46]. The subject has been tried to be explained by different anticancer mechanisms of LIDC, such as: induction of bioelectric forces in the tumour [16,19]; changes in bioelectric potential [47]; modifications of pH and temperature in the tumour [48,49]; changes in transmembrane potential of tumour cells [50,51]; ionization of tumour tissue [52]; production of toxic substances from the electrochemical reactions [22]; deposition of electrode material into tumour [53]; stimulation of immune system [54]; extraction of water tissue by electroosmosis [22,49]; and electrochemical reactions mainly referred to those involving reactive oxygen species.

These possible anticancer mechanisms of LIDC are proposed from different experimental conditions established by each author. In each of these studies, it has been reported a use of certain amount of LIDC with a particular exposure time and with a specific electrode configuration. In studies using more than one LIDC and exposure time applied, that combines this method with other therapeutic techniques, was not observed the complete remission in all tumours except in a few animals.

From the above, it is concluded that there is no agreement about the parameters employed in this treatment nor these are optimized. The establishment of optimal parameters by executing several experiences requires a plenty of time and material resources. One way that gives us in a several minutes or hours the appropriate electrode configuration with

the respective applied LIDC can be through mathematical modelling.

In oncology, mathematical modelling are used in simulation: in the kinetics of tumour growth [55-58], in spatial and temporal growth of tumour avascular phase [59,60], in interaction and competition between tumour and immune system [60,61] among others. Richards, Weibull, Bertalanffy and Gompertz logistic models are applied to describe the kinetics of tumour growth, where the latter is the most employed [55,56].

In the field of electrotherapy, mathematical modelling are focussed in the explanation of different processes that are induced in the tumour after the application of LIDC, such as: pH modifications [21]; physicochemical reactions around electrodes [62]; potential dissipation in the tumour after applying LIDC [63]. Also in this subject, are employed modellings to describe the kinetics of treated tumours after applying LIDC, [16,64] as well as drawing configurations of the respective electrodes [65]. None of these models relate the electrical electrotherapy parameters with the tumour kinetics. Furthermore they do not discuss the potential distributions, electrical field intensity and electric current density as a function of the differences between conductivities and permittivities existent between the tumour and the healthy surrounding tissue. The parameters of the electrode configuration (position, number and polarity of the electrodes, size and geometry) that allows the maximum tumour destruction giving the less damage possible to body need to be also improved.

Despite the promising results of electrotherapy in malignant and benign tumours there are two fundamental reasons that prevent its establishment with clinical oncology as a therapeutic procedure:

1. The poor understanding of the LIDC anticancer action mechanism;
2. The lack of standardization of therapy by tumour type, size and stage. The last reason results from not being established the range of LIDC yet nor the optimal configuration of electrodes that can destroy the tumour and simultaneously damaging the body as less as possible.

Obviously, these issues suggest that is necessary to propose experiments and mathematical modelling to deal with these questions. The description of tumour volume behaviour and electric current density established by an electrode system with a continuous current as a function of kinetic parameters of the cancer or electric of the technique will allow the standardization of this experimental therapy. The modelling of potential distributions, electric field intensity and electric current density, established with several electrode configurations (e.g. circular arrangement, elliptical, etc.) in tumour and healthy surrounding tissue, when visualized with mathematical programs is, according to the authors, and as much as it is informed other general and specific experimental resolution for these problems.

The analysis/study in experimental and/or theoretical terms of tumour volume behaviour and electric current density that is established by a set of electrodes with electric current as a function of kinetic and electric parameters that describe the kinetics growth of cancerous tumours and physic-chemical electrotherapy characteristics used in its possible treatment are an objective of the authors which will be reported in the near future.

2. Conclusions

Studies about electricity began with Thales in 600 BC and twenty three centuries later important developments were observed in the field of bioelectricity, thanks to work of Galvani, Volta, Ampere, Ohm, among others.

The use of electrotherapy in medicine starts in the 70s of XVIII century, where it was used for cure of some diseases. In 1776, Eason proposed for the first time an important role of electricity for cancer treatment [18]. Since this work and other similar, the use of continuous electric current during cancer treatment and the respective technological advances associated with this application, has resulted in a huge growth of *in vitro* studies, animals and humans about anticancer effect of LIDC.

During these last decades, have been highlighted groups of doctors, biophysicists, biologists, mathematicians in China, Brazil, Cuba, Germany, Canada, Slovenia, Sweden, etc..

All these studies show the diversity of criteria on how to use and combine the different parameters that configure the electrotherapy. The lack of agreement referred to use of therapy parameters prevents its further implementation in clinical oncology.

References

[1] R.S. Cotran, S.L. Robbins. *Patologia Estructural y Funcional – Séptima Edición*. Ed. Elsevier, Saunders, Madrid (2005).

[2] S.M. Cohen, L.L. Arnold. *J. Toxicol. Pathol.* **21**, 1 (2008).

[3] Y. Kanai. *Pathol. Int*., **58**, 544 (2008).

[4] A. Koliopanos, C. Avgerinos, C. Paraskeva, Z. Touloumis, D. Kelgiorgi, C. Dervenis. *Hepatobiliary Pancreat. Dis. Int*. **7**, 345 (2008).
[5] S. Toyokuni. *IUBMB Life* **60**, 441 (2008).
[6] World Health Organization (WHO). Available in: http://www.int/mediacentre/factorsheets/fs2977es/index.html. Last update: July 2008.
[7] Union for International Cancer Control (UICC). Available in: http://www.uicc.org/index.php?option=com_content&task=view&id=13&Itemid=113. Last update: September 2008.
[8] I. Hoshino, H. Matsubara, A. Komatsu, Y. Akutsu, T. Nishimori, Y. Yoneyama, K. Murakami, H. Sakata, K. Matsushita, Y. Miyazawa, R. Brooks, M. Yoshida, T. Ochiai. *Oncology* **75**, 113 (2008).
[9] C. Ruegg, N. Mutter. *Bull. Cancer* **94**, 753 (2007).
[10] S.D. Xiang, K. Scalzo-Inguanti, G. Minigo, A. Park, C.L. Hardy, M. Plebanski. *Expert Rev. Vaccines* **7**, 1103 (2008).
[11] J.I. Toohey. *Cancer Lett*. **263**, 164 (2008).
[12] H. Tanaka, K. Kageyama, R. Asada, N. Yoshimura, N. *Exp. Oncol*. **30**, 143 (2008).
[13] M. Sadadcharam, D.M. Soden, G.C. O'Sullivan. *Int. J. Hyperthermia* **24**, 263 (2008).
[14] N. Schaefer, H. Schaefer, D. Maintz, M. Wagner, M. Overhaus, A.H. Hoelscher, A. Türler. *J. Surg. Res*. **146**, 230 (2008).
[15] D.S. Yoon, Y.M. Ra, D.G. Ko, Y.M. Kim, K.W. Kim, H.Y. Lee, Y.L. Xin, W. Zhang, Z.H. Li, H.V. Kwon. *Journal of Breast Cancer* **10**, 162 (2007).
[16] L.C. Bergues *La electroterapia una nueva alternativa para el tratamiento de tumores malignos*. Estudios preclínicos. Tesis de doctorado (2003).
[17] Y. Xin The development of electrochemical therapy in China. Proceedings of the 8th Congress on tumours of the International Association of Biological Closed Electric Circuits, Nanning, China, September 21-23, pp. 4-8 (2004).
[18] H. Hiller. *Arch. Phys. Ther*. **17**, 67 (1965).
[19] M.K. Schauble, M.B. Habal, H.D. Gullick. *Arch. Path. Lab. Med*. **101**, 294 (1977).
[20] B.E.W. Nordenström. *I.R.C.S. Med. Sci*. **6**, 537 (1978).
[21] P. Turjanski, N. Olaiz, P. Abou-Adal, C. Suarez, M. Risk, G. Marshall. *Electrochim. Acta* **54**, 6199 (2009).
[22] A.K. Vijh. *Modern Aspects of Electrochemistry* **39**, 231 (2006).
[23] M. Kurokawa, H. Sakagawi, F. Kokubu, H. Noda, M. Takeda, M. Adachi. *J. Cancer Res. Clin. Oncol*. **123**, 370 (1997).
[24] V.F. Veiga, L. Nimerichter, C.A. Teixeira, M.M. Morales, C.S. Alviano, M.L. Rodrigues, C. Holandino. *Cell. Biochem. Biophys*. **42**, 61 (2005).
[25] V.F. Veiga, C. Holandino, M.L. Rodrigues, M.A. Capella, S. Menezes, C.S. Alviano. *Bioelectromagnetics* **21**, 597 (2000).
[26] B. Tang, L. Li, Z. Jiang, Y. Luan, D. Li, W. Zhang, E. Reed, Q.Q. Li. *Int., J. Oncol*. **26**, 703 (2005).
[27] M. Wartenberg, N. Wirtz, A. Grob, W. Niedermeier, J. Hescheler, S.C. Peters, H. Sauer. *Bioelectromagnetics* **29**, 47 (2008).
[28] K.H. Li, Y.L. Xin, Y.N. Gu, B.L. Xu, D.J. Fan, B.F. Ni. *Bioelectromagnetics* **18**, 2 (1997).
[29] S.A. Wemyss-Holden, A.R. Dennison, D.P. Berry, G.J. Maddern. *Journal of Hepato-Biliary-Pancreatic Surgery* **11**, 97 (2004).
[30] H. Von Euler, J.M. Olsson, K. Hultenby, A. Thörne, A.S. Lagerstedt. *Bioelectrochemistry* **59**, 89 (2003).
[31] C.K. Chou, J.A. McDougall, C. Ahn, N. Vora. *Bioelectromagnetics* **18**, 18 (1997).
[32] M. Wójcicki, R. Kostyrka, B. Kaczmarek, J. Kordowski, M. Romanowski, M. Kaminski, J. Klonek, S. Zielinski. *Hepatogastroenterology* **46**, 278 (1999).
[33] H. Von Euler. *Electrochemical treatment of tumours*. Doctoral thesis. Swedish University of Agricultural Sciences, Uppsala (2002).
[34] C.K. Chou. *Bioelectromagnetics* **28**, 3 (2007).
[35] International Association for Biological Closed Circuits (IABC), available in http://www.iabc.readywebsites.com/. Last actualization: March 2008.
[36] B.P. Patel, U.M. Rawal, R.M. Rawal., S.N. Shukla, P.S. *Am. J. Clin. Oncol*. **31**, 454 (2008).
[37] R.L. Ren, N. Vora, F. Yang, J. Longmate, W. Wang, H. Sun, J.R. Li, L. Weiss, C. Stand, J.A. McDougall, C.K. Chou. *Bioelectromagnetics*, **22**, 205 (2001).
[38] H. Ando, K. Ito, L. Wang, K. Hibi, K. Hidemura, T. Yamazaki, Y. Kasai, S. Akiyama, A. Nakao *Anticancer drugs* **13**, 321 (2002).
[39] G. Serša, R. Golouh, D. Miklavčič. *Anti-Cancer Drugs* **5**, 69 (1994).
[40] L. Samuelsson, L. Joensson, I.L. Lamm, C.J. Linden, S.B. *Acta Radiol*. **32**, 178 (1991).
[41] L. Xie, C.A. Sun. *Int. J. Hyperthermia* **22**, 607 (2006).
[42] D. Maintz, R. Fischbach, N. Schafer, A. Turler, H. Kugel, H. Schafer, K. Lackner. *Rofö Forstschr. Geb. Röntgenstr. Neuen Bildbeg Verfahr* **173**, 471 (2001).
[43] J. Larkin, D. Soden, C. Collins, K. Tangney, J.M. Preston, L.J. Russel, A.P. McHale, C. Dunne, G.C. O'Sullivan. *Eur. J. Cancer* **41**, 1339 (2005).
[44] X.Z. Lin, C.M. Jen, C.K. Chou, C.S. Chou, M.J. Sung, T.C. Chou. *Dig. Dis. Sci*. **45**, 509 (2000).
[45] C. Dobbins, S.A. Wemyss-Holden, J. Cockburn, G.J. Maddern. *J. Surg. Res*. **144**, 111 (2008).
[46] H. Von Euler, K. Strähle, A. Thörne, G. Yongping. *Bioelectrochemistry* **62**, 57 (2004).
[47] C.E. Humphrey, E.H. Seal. *Science*, **130**, 388 (1959).
[48] L. Colombo, G. González, G. Marshall, F.V. Molina, A. Soba, C. Suarez, P. Turjanski. *Bioelectrochemistry* **71**, 223 (2007).
[49] A. Vijh. *Int. J. Hydrogen Energy* **29**, 663 (2004).
[50] A.T. Esser, K.C. Smith, T.R. Gowrishankar, J.C. Weaver. *Technol. Cancer Res. Treat*. **6**, 261 (2007).
[51] L. Vodovnik, D. Miklavčič, G. Serša. *Med. & Biol. Eng. & Comput*. **30**, CE21 (1992).
[52] F. Zhu, S. Tan, J. Lin. Effects of direct pulse on tissues of tumours in mice. Proceedings of the 18th Annual International Conference. IEEE Engineering in Medicine and Biology, Amsterdam, 35-36 (1996).
[53] H.B. Kim, S. Ahn, H.J. Yang, S.B. Sim, K.W. Kim. *Micron*, **38**, 747 (2007).
[54] G.Serša, V. Kotnik, M. Cemazar, D. Miklavčič, A. Kotnik. *Anti-Cancer Drugs* **7**, 785 (1996).
[55] A. Behera, C. O'Rourke. *Braz. J. Phys*. **38**, 272 (2008).
[56] D. Grecu, A.S. Carstea, A.T. Grecu, A. Visinescu. *Romanian Reports in Physics* **59**, 447 (2007).

[57] J. Bayani, J. Paderova, J. Murphy, B. Rosen, M. Zielenska, J.A. Squire. *Neoplasia* **10**, 1057 (2008).
[58] E. Mehrara, E. Forssell-Aronsson, H. Ahlman, P. Bernhardt. *Cancer Research* **67**, 3970 (2007).
[59] H.M. Byrne. *Nature Reviews/Cancer* **10**, 223 (2010).
[60] L. Preziosi. *Chapman & Hall / CRC*, New York (2003).
[61] A.D'Onofrio. *Mathematical and Computer Modelling* **47**, 614 (2008).
[62] P. Turjanski, A. Soba, C. Suarez, L. Colombo, G. González, F. Molina, G. Marshall. *Mecânica Computacional* **261**, 3458 (2007).
[63] T. Kotnik, D. Miklavčič. *Bioelectromagnetics* **21**, 385 (2000).
[64] D. Miklavčič, T. Jarm, R. Karba, G. Serša *Math. Comp. Simulation* **39**, 597 (1995).
[65] S. Čorović, M. Pavlin, D. Miklavčič. *Biomed. Eng. Online* **6**, 37 (2007).