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Emerging diagnostic and therapeutic applications of non-ionising electromagnetic radiations in Oncology

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Abstract

In this paper, we review the scientific literature dealing with many potentially interesting applications of non-ionizing electromagnetic radiations, in the radio-frequencies range, in oncology. Despite their mechanisms of action are still largely unrecognised and clinical trials haven't still been carried out to support their efficacy with respect to the natural course of the disease, these technologies are usually characterized by very favorable safety profiles both for patients and operators. We reason that denying their use to oncology patients at any stage of the disease appears a discriminatory act in comparison with patients in other areas of medicine, such as rehabilitation, aesthetic and sports medicine, where these technologies are routinely applied, instead.

We envision their application in a complementary approach, in order not to compromise compliance with currently validated and proven therapeutic protocols.

Introduction

Electromagnetic radiation such as ultraviolet light, X-rays and gamma rays are employed in a number of widely known applications in medicine. In addition, an endless list of instruments employ non-ionizing electromagnetic radiations (visible and infrared light, microwaves and radiowaves) for medical purposes [1].

In this paper, we focus on innovative techniques that employ electromagnetic radiation in the range of radio frequencies RFs with or without source modulation, with the exception of well-known techniques that use them for nuclear magnetic resonance imaging [2], and therapy. Notably, however, the so called cytotron has recently earned the status of "breakthrough therapy" by the FDA for the treatment of various types of solid tumors and multiple sclerosis [3].

RFs interact with vibro-rotational states of small molecules, such as water, inducing localized heating; but also with vibro-rotational states of macromolecular complexes that form integral parts of sensory systems of living beings [4-7].

In fact, low power density (10 mW/cm^2 or less) waves of millimeter wavelength (corresponding to frequencies of a few tens of GHz), although too low to cause skin overheating or deep tissue penetration [6,8] showed effects on the nervous system [9] and on the immune system [10]. Positive findings have been recorded in analgesia, [11] and on certain tissues typical of psoriasis, eczema and tumor lesions [12].

Sub-millimeter RFs (at frequencies from 300 GHz up to 30 THz), that resonate with objects of micrometric dimensions such as cells, their organelles and even the macromolecules within them, [13] have little penetration into tissues because they are strongly absorbed by the water of the surface [14,15], but have been used in dermatology and dentistry [16,17] and some dermatological oncological lesions have been treated using these frequencies [18-20].

One important aspect of RFs is that they should essentially have very favorable safety profiles according to the fact that many devices that populate our daily life employ them.

These are, for instance, radio, television , cordless telephones, cell phones, cellular antennas, satellite telephones, WiFi devices, Bluetooth®, etc. [21] Suspected carcinogenic effects of RFs have so far never been demonstrated, although some correlation has been observed between an increase in leukemias and brain tumors in populations exposed to high intensity electromagnetic fields and radiations, even if in the non-ionizing range of frequencies. [22,23] Studies on experimental animals have shown so far unclear results. In a large study published in 2018 by the US National Toxicology Program (NTP) and the Ramazzini Institute in Italy, on rats and mice irradiated throughout their lifetime from birth, showed only a modest risk increase for schwannoma formation in male rats. The same risk was not observed for female rats nor for male or female mice [24].

Providing the many beneficial effects of RFs which are reviewed as follows, denying to oncology patients at any stage of the disease the possibility of using them, would be a discriminatory act in comparison with other patients in areas such as rehabilitation, aesthetic and sports medicine.

We envision the use of RFs based technologies in a complementary medicine approach, recommending that their use would not induce

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patients to lose compliance with currently validated proven therapeutic protocols.

RF in diagnostics

Greater vascularization, blood flow and water content in tumor lesions can determine a variation in the propagation, reflection and attenuation of micro and radio waves compared with surrounding healty tissues [25]. Tumors have higher dielectric properties than corresponding healthy tissues, which can be detected by frequency waves up to 1 GHz up to a few GHz, with higher frequencies providing better resolution but less penetration. Diagnostic imaging based on non-ionizing electromagnetic radiation would therefore be a non-invasive, harmless diagnostic method compared to current methods that use higher energy (ionizing) radiation, instead.

Some experimental prototypes for electrical impedance based tomography have recently appeared in the literature [26,27]. A number of clinical studies have been carried out by breast cancer research groups [28] with equipment at different frequencies (1-8 GHz) and the results obtained compared with other well-known diagnostic methods, such as mammography and ultrasound. Diagnostic capacity was similar to mammography (74% vs 78%) [25] and larger studies are ongoing.

Thermal effects of RF

RFs do not have enough energy to remove electrons from atoms and molecules; and their absorption takes place by resonance with vibro-rotational of molecules generating thermal heating effects, such as the well known cooking effect of the microwave oven. In fact, various instruments exploit thermal effects of RFs [29].

Diathermy uses RFs in the 1-100 MHz range (most often short waves at 27.2 MHz), in continuous or pulsed mode. Microwaves in the 434-915 MHz range (most often 915 MHz) have also been used to generate mild heating in living tissues. The pain-relieving effect of diathermy is normally used in physiotherapy and some meta-analyses have shown very interesting effects, for example in knee osteoarthritis, with more pronounced effects with pulsed waves rather than with continuous ones [30] and with deep rather than superficial heating [31]. Randomized double-blind studies with high numbers of cancer patients are not available to date but beneficial effects both in terms of pain reduction and restoration of muscle function have been demonstrated in other clinical settings [32]. Diathermy is clearly associated with increased local blood flow secondary to heating above 41.5°C. The increase in blood flow increases nutrients, oxygen, elasticity, promotes pH normalization and has analgesic, metabolic-modulating and neurobiological effects [33,34]. Short-wave diathermy has been observed to be more effective than the medium-wave one in determining greater blood flow by means of echo-doppler measurements [30].

Hyperthermia uses higher temperature increase, in the 40-45°C range, to kill cancer cells, in combination with conventional treatments [35,36]. In fact, hyperthermia can even make cancer cells more sensitive to radiotherapy and chemotherapy treatments [37]. Hyperthermia can be applied locally or to the entire body depending on the size and location of the tumors. Special probes are used for the treatment of deep tissues, in areas of less than 5 cm sections, to eliminate tumor cells and adjacent vessels [35]. Another use of hyperthermia is to warm the blood of patients suffering from tumors disseminated with circulating cells. Whole-body hyperthermia is practiced through heating blankets, immersion in hot water and thermal chambers. This type of hyperthermia favors the action of the immune system [38].

Electrosurgical ablation takes advantage of even more pronounced heating, with temperature increases up to 70-75°C. The RF are administered locally by inserting an electrode into the tissues to locally destroy it. In some cases, the destruction of nerve endings is also practiced reducing chronic pain. This technique is widely used in the micro-surgical field, in neurosurgery and ophthalmic surgery; where RF are usually applied to small lesions by means of probes surgically inserted by radiological control (ultrasound, MRI, CT). It has been currently applied to liver [39], kidney [40] and lung lesions [41]. In Japan, RF ablation is widely used in liver tumors and other forms of solid neoplasms. In a phase I study, localized breast tumors less than 2 cm in diameter were completely removed in 90% of cases and a phase II study is evaluating the effects on multiple patients [42].

Nanoparticle mediated thermal effects of RF

As an alternative to the use of probes, it has been proposed to use nanoparticles to pick up RFs. For this purpose, superparamagnetic iron oxide nanoparticles have been used to pick up RF in a very efficient and localized way. Other nanoparticle materials include gold, cobalt oxide and carbon, in addition to the so-called "quantum dots" [43]. RFs used in magnetic hyperthermia are of the order of kHz up to 1 MHz [44]. The degree of heating is given by a specific absorption rate based on the magnitude and frequency of the magnetic field, the material of the nanoparticles, their shape, crystallinity, aggregation and viscosity [45]. Larger particles respond to external fields faster and are better eliminated from the bloodstream [46]. The resulting so called magnetic hyperthermia has been shown to stimulate the oxygenation of cancer cells which increases their radiosensitivity [47].

Magnetic hyperthermia has been used in conjunction with radiotherapy in the experimental treatment of recurrent glioblastoma multiforme and breast cancer [47,48]. This made it possible to reduce radiation doses and side effects. However, in clinical trials the effectiveness of this approach has been shown to be quite modest [49]. Other clinical trials are ongoing in various types of neoplasms [50].

Non thermal RF effects

Electromagnetic fields (EMFs) can act on cellular chemotactic communications and gene expression [51]. Low frequency pulsed EMF have been shown to influence root growth of plants at frequencies of 60 Hz with fields of 350V /m and 450V / m, [52] metabolism of fermenting yeast cells, increasing ethanol production by 25% - 30% [53] and even cause apoptosis of tumor cells [54].

An interesting study reported the use of alternated electric fields produced by wearable nanogenerators installed at the edge of wounds, emitting in a synchronized manner with the respiratory activity of experimental animals. Pulses could vary in amplitude based on the activity of the rats. The authors monitored macro- and microscopic wound healing, as well as molecular markers. The wounds treated with alternating electric fields healed on average in 3 days vs 12 days on the same subjects. The healing activity was associated with the migratory, proliferative and trans-differentiative activity measured in vitro of 3T3 fibroblasts. Conventional AC electric field generators of constant frequency and amplitude had a minor effect on fibroblasts and also caused high concentrations of ROS, much higher than those produced by nano-stimulators [55].

Methodologies that use pulsed electromagnetic fields (PEMFs), pulsed radiofrequency fields (PRF) or pulsed radiofrequency energy (PRFE) have been proposed for clinical applications [56].

One area where studies on these techniques are available is that of wounds treatment, where the PEMFs application appears to accelerate healing, especially when associated with pharmacological interventions [57]. Reviews are also available on the use of pulsed 27.12 MHz generators on the treatment of various types of ulcers [58-60].

In the treatment of inflammation and pain associated with osteoarthritis, rectangular wave pulses have been tested and shown different results depending on the frequency and flux density [61]. PEMFs have also been tested in the treatment of cardiac arrhythmias [62], post-operative pain [4], bone fracture and soft tissue wounds, [63] and in some oncology trials [64]. Interestingly, exposure to PEMFs has modulatory effects on the components of the immune system [65]. As regards to macrophages, a response to both static and pulsed electromagnetic fields at low intensity was noted with an increase in oxidative stress and an increase in phagocytic activity which is the basis of a possible therapeutic effect on neurodegenerative diseases with an autoimmune component [66].

A novel non-invasive method, named TTfields, employs pulsed electromagnetic generators applied locally outside interested areas of the body, to reverse the polarity of tumor cells with frequencies in the 100-300 kHz range. The frequency used for gliomas is, for instance, 200 kHz [67]. Preclinical studies have shown that TTfields are effective against various types of neoplasms and the FDA approved this treatment in 2015 as first-line treatment for patients with glioblastoma multiforme (GBM) in combination with the drug temozolomide (TMZ) [68,69]. The effect of these pulsed electric fields is also used in other cancers with different pulsation frequencies. The fields are very low intensity, they interfere with the formation of microtubules during mitosis and mitosis. Sensitivity to pulsed electric fields is greater for rapidly dividing cells. Since TTFields affect polar molecules and electrically charged organelles, they counteract the formation of the mitotic spindle. The result is an aberrant mitosis and a consequent caspase-dependent apoptosis. Other interpretative models see TTfields as a cause of molecular ion aggregation with consequent compromise of various cellular structures during replication [68,70-72]. Some subsequent clinical studies have prompted guidelines on the use of this technology [73-75]. Recently, the international phase 3 study EF-14 showed an increase in overall survival of 5 months of patients treated with TTfields and temozolomide compared to patients treated with chemotherapy alone. Better quality of life and lower incidence of side effects were observed in the TTfields group [76]. Trials have also been started on TTfiels in other neoplasms with typically poor prognosis such as: low-grade gliomas, brain metastases of solid tumors, lung and pancreatic tumors. However, the antimitotic activity of TTfields requires continuous application and the treatment involves use for more than 18 hours a day [77]. Therefore, portable devices are being developed that can allow that kind of portability.

Another technique, named biofeedback, defined as a reduction in the radial amplitude of the electromagnetic pulse administered following the interaction with the target organism, has been prompted in the oncology field by involuntary discovery performed during a study on insomnia carried out by Barbault et al. [78]. The involuntary observation was that certain specific frequencies are effective in reducing cell proliferation in cancer patients [79]. Patients with the same tumor pathology exhibited biofeedbacks at the same frequencies. 163 patients with confirmed diagnosis were therefore treated with a carrier frequency of 27.12 MHz RF-EMF (widely approved for medical use) and various amplitude modulations thereof, between 0.1 Hz to 114 kHz. Most of the frequencies (57-92%) were specific to a single tumor type. Only 4 frequency modulations (1873.5 Hz, 2221.3 Hz, 6350.3 Hz, and 10,456.4 Hz) were common to several cancers, such as breast cancer, hepatocellular carcinoma (HCC), prostate cancer, and pancreatic cancer [79].

Another interesting technology employed amplitude modulated RFs for the treatment of cancer. Costa et al. in an open-label phase I / II study administered through a low-power emitter for oral use (<2 W / kg) these types of RFs to patients with liver cancer [80]. Treatment lasted 1 hour 3 times a day. Treatment stopped disease in 34% of patients for over 6 months, median overall survival was 6.7 months (95% CI 3.0-10.2) months with no median progression of 4.4 months (95% CI 2.1-5.3). In addition, one complete response and three partial responses were recorded. While very interesting, these results were the work of a single research group and have not been replicated by other authors independently.

Electroporation (EP) with RF

Electroporation consists in increasing the permeability of the cell membrane in order to insert drugs and / or genes inside the cancer cells. This is done by exposing the cells to electric pulses of high intensity (amplitude) and short duration, causing the formation of aqueous pores in the cell membrane [81]. The mechanism of aqueous pore formation is currently not well understood at the molecular level and the opening of the pores occurs in times of nano-microseconds, with their closing taking place in longer times, from seconds to minutes [82]. Pulses several milliseconds long are used for gene transfer and transfection with viruses or plasmids to DNA [81]. Similarly fast electroporation can be used to administer drugs very fast to cells and allows the cell membrane to be restored. Intracellular drug transfer obtained in this way can reduce systemic side effects, favoring the subsequent action of the immune system [83]. Long irreversible electroporation (IRE) uses voltage pulses to induce cell death, instead, through permanent membrane damage and loss of homeostasis. Although the ablative effect is not selective with respect to non-cancer cells, the technique has been approved by the FDA for some particularly aggressive diseases of the pancreas [84,85].

Different protocols of electroporation approaches have been tested based on the morphological and tissue characteristics of tumors [86] Mir et al. have used this method to deliver bleomycin into cancer cells, in an approach named electrochemotherapy (ECT). [87-89] Complete tumor regression was observed in 73.7% of treated nodules with an overall response of 84.8% for 6 months after a single ECT session [90]. In 2019, about 150 research centers in Europe applied ECT for the treatment of primary and metastatic cancers and very promising results were published in multicenter studies. Complete responses were 30-65% at 1 year and disease control between 30% and 90%, depending on the type of tumor [91]. ECT treatment can induce immunogenic cell death and an immune response against the remaining tumor cells [92]. Case and retrospective studies have shown that the combination of ECT with immunotherapy can induce abscopal effects in nodules not treated with ECT. This suggests the establishment of a systemic immune mediated response and suggests the usefulness of carrying out clinical studies in which ECT is combined with modern immunotherapy, which is currently very popular [93].

A variant of EP uses calcium instead of bleomycin or cisplatin chemotherapy drugs, and induces cell death via necrosis due to the introduction of high concentrations of intracellular calcium. In vitro and in vivo studies show the effectiveness of this "calcium EP" [94]. The first randomized phase II trial included 7 patients with a total of 47 cutaneous metastases from breast cancer and malignant melanoma [95]. Patients were treated with Ca2 + (0.5-1 mL / cm^3 of tumor volume) or bleomycin before electroporation. Calcium treatment achieved similar responses to bleomycin (72% vs 84%), but fewer side effects (38% vs 68%) [95]. ECT is therefore effective in the local treatment of cutaneous and subcutaneous metastases of melanoma. ECT also appears useful in patients with inoperable tumors or non-responsive to standard chemotherapy protocols. Strategies combining immunotherapy, gene transfer and radiotherapy to ECT are strongly warranted.

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