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Extremely Low Frequency Magnetic Field Alters Cytotoxicity of Irinotecan in Glioblastoma: A Preliminary Observation

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Abstract

Objective: Exposure to extremely low-frequency electromagnetic fields (ELF-EMFs) emitted from electric appliances used in daily life may cause various changes at the cellular level. Glioblastoma multiform (GBM) is an aggressive brain cancer resulting in high mortality. Despite advances in treatment methods, GBM has remained an incurable disease. It has become important that necessary precautions are taken to overcome factors that may reduce the efficiency of antineoplastic agents used for GBM patients. Irinotecan, an antineoplastic agent, is one of the second line drugs for GBM patients. The aim of this preliminary research was to examine the impact of ELF-EMF on irinotecan cytotoxicity in GBM cells.

Method: GBM cells (U87) in the control group were only treated with irinotecan (0, 1, 2, 10, 25, 50, 75, and 150 μM). ELF-EMF (50 Hz, 1 mT) and irinotecan were applied simultaneously for 1 h to similar cells in the study group. Cytotoxicity was determined via XTT assay.

Results: While the IC50 (half maximal inhibitory concentration) value was 14.31 μM in the control group, and 20.51 μM in the study group.

Conclusion: The results of the study indicated that ELF-EMF reduced the efficiency of irinotecan in the U87 cells. Therefore, patients undergoing chemotherapy with irinotecan should be given more attention so as to avoid ELF-EMFs. The effects of ELF-EMF on irinotecan cytotoxicity in U87 cells were determined through an exactly unknown mechanism. Further studies on ELF-EMFs and irinotecan cytotoxicity are required to illuminate the topic.

Keywords: Extremely low-frequency electromagnetic field, Glioblastoma multiform, Irinotecan, Cytotoxicity.

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Çok düşük frekanslı manyetik alan, glioblastomda irinotekan sitotoksisitesini değiştirir: Bir ön gözlem

Öz

Amaç: Günlük hayatta kullanılan elektrikli cihazlardan yayılan çok düşük frekanslı elektromanyetik alanlara (ELF-EMF) maruz kalınması, hücresel düzeyde çeşitli değişikliklere neden olabilmektedir. Glioblastoma multiform (GBM), yüksek mortalite ile sonuçlanan agresif bir beyin kanseridir. Tedavi yöntemlerindeki ilerlemelere rağmen, GBM tedavi edilemeyen bir hastalık olarak kalmıştır. Diğer taraftan, GBM hastalarında kullanılan antineoplastik ajanların etkinliğini azaltabilecek faktörlere karşı önlem alınması da önem kazanmıştır. Antineoplastik bir ajan olan irinotekan, GBM hastaları için kullanılan ilaçlardan biridir. Bu ön çalışmanın amacı, ELF-EMF'nin GBM hücreleri üzerinde irinotekan sitotoksisitesi üzerindeki etkisini incelemektir.

Yöntemler: Kontrol grubundaki GBM hücrelerine (U87), farklı konsantrasyonlarda irinotekan (0, 1, 2, 10, 25, 50, 75 ve 150 μM) uygulandı. Çalışma grubundaki hücrelere ise, ELF-EMF (50 Hz, 1 mT) ve irinotekan, 1 saat süreyle eş zamanlı uygulandı. Sitotoksisite, XTT testi ile belirlendi.

Bulgular: IC50 (yarı-maksimum inhibisyon konsantrasyon) değeri, kontrol grubunda 14,31 μM iken, çalışma grubunda 20,51 μM olarak bulundu.

Sonuç: Çalışmanın sonuçları, ELF-EMF'nin irinotekanın U87 hücreleri üzerindeki etkinliğini tam olarak bilinmeyen bir mekanizma ile azalttığını gösterdi. Bu nedenle, irinotekan ile kemoterapi alan hastaların ELF-EMF'lerden kaçınmak için daha fazla dikkat göstermeleri gerekmektedir. ELF-EMF'lerin irinotekan sitotoksisitesi üzerindeki etkinliğini hangi mekanizmalar aracılığı ortaya koyduğunu göstermek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Çok düşük frekanslı elektromanyetik alan, Glioblastoma multiform, İrinotekan, Sitotoksisite.

INTRODUCTION

It is a well-known fact that cancer has become one of the most significant causes of death worldwide. The primary method among diverse cancer treatments is still chemotherapy due to its high efficiency[1]. Glioblastoma multiform (GBM), a type of cancer, is the most commonly observed and the most aggressive type of brain tumor that arises from the glial cells within the central nervous system. It was reported that an annual incidence of 5.4 people per 100,000 in Europe have been diagnosed with GBM[2]. Various therapeutic strategies involving surgical removal, radiotherapy, and chemotherapy are performed to treat GBM. Despite advances in treatment methods, GBM has remained an incurable disease. The average rate of survival for an adult who has GBM is very low, comprising between 10 and 16 months[2]. This situation has prompted the scientific researchers to explore the field of effective therapy for GBM and take necessary precautions to overcome factors that reduce the efficacy of treatment methods used for GBM patients. Irinotecan is a chemotherapeutic camptothecin derivative that acts as an inhibitor of topoisomerase I, which is a crucial nuclear enzyme needed for DNA transcription[3]. Irinotecan has partial capacity of crossing the blood-brain barrier (BBB) and it has a toxic effect against central nervous system tumors[1]. The antitumor activity of irinotecan has been proven on glioblastoma cells with multidrug resistance. On the other hand, its efficiency appears to be improved when used in combination with other drugs, such as temozolomide and bevacizumab[4]. Irinotecan causes severe side effects, just as other chemotherapeutic drugs do, in organisms. As a result, a dose reduction was recommended for the use of irinotecan to reduce its side effects[5].

Technological advances and the growing demand for electric energy, and thus the growing number of artificial sources of

electromagnetic fields (EMFs), has led to intensive exposure to EMFs. An EMF frequency below 300 Hz is classified as extremely low frequency (ELF) fields in the scientific literature. The highest intensity of ELF-EMFs can be found in near proximity to electric appliances in the home and workplaces or medical devices in hospitals, and these fields may reach up to a few mT[6]. A great number of studies have demonstrated that exposure to ELF-EMF, even at a low intensity, may cause various changes at the cellular level[6]. Changes in proliferation and differentiation of cells[7], alterations in the membrane properties, such as permeability to Ca2+[8], and modifications in the cytoskeletal organization are among the biological effects induced by EMFs[9]. The effects of ELF-EMF on tissue repair have been reported in a recent study[10]. Moreover, it has been argued that ELF- pulsed electromagnetic fields (PEMFs) induce tumor growth inhibition[11]. These effects depend on the physical characteristics of EMFs and the duration of exposure by the subject[12]. In the related literature, evidence exists that ELF-EMFs can extend the survival time of patients with advanced malign tumors and can alleviate their general symptoms[13]. Various clinical research has demonstrated that exposure to ELF-PEMFs by cancer patients did not result in any side effects[13]. It was also demonstrated that using certain EMF signals in the treatment of advanced hepatocellular carcinoma was able to stabilize the disease, and it was even able to produce positive responses, partially at least, in a subgroup of these patients[14]. In addition, it was reported that exposing HL-60 cells to an ELF-EMF (50 Hz, 20 mT, sinusoidal) resulted in growth inhibition[15]. Therefore, it was indicated that some of these influences of ELF-EMFs may be used for medical treatment[16]. On the other hand, several studies have indicated that exposing malignant tumors to ELF-PEMFs (50 Hz; 0.5–1.0 mT) enhances free radicals released by the cells[17] and causes dysregulation in apoptotic processes[18]. In addition, it should be also considered that the response of cancer cells to ELF-EMFs will be different to some degree dependent on the EMF characteristics, which include the amplitude, waveform, frequency, and length of the exposure.

It was reported that ELF-EMFs influence the potential efficiency of some chemotherapeutic drugs on cancer cells[19]. The effects of ELF-EMFs on the cytotoxicity of various chemotherapeutic drugs were explored on various cancer cells and different results were reported depending on the characteristics of the experimental model and applied EMFs. Several studies have indicated that ELF-EMFs promote the cytotoxicity of some chemotherapeutic drugs[18,20], whereas others have demonstrated that exposure to ELF-EMFs inhibits the cytotoxicity[21].

The effect of ELF-EMFs on irinotecan cytotoxicity is still unknown. Therefore, it was aimed herein to investigate the possible synergistic or antagonistic influence of ELF-EMFs on irinotecan cytotoxicity in human GBM cells (U87). Irinotecan application doses were determined according to similar studies in the literature, which reported that irinotecan shows important toxic activity for these doses in U87 cells[22]. The frequency and intensity of the applied EMFs in this study were similar to those of the EMFs measured in near proximity to most medical devices or electrical appliances in homes, workplaces, and hospitals[23]. Moreover, the characteristics of the ELF-EMFs were adjusted according to the efficiency reported in previous studies on cancer cells[18].

METHODS

The study designed with a control and exposure group. The U87 cells used in the control group were only treated with irinotecan at different concentration, such as 0, 1, 2, 10, 25, 50, 75, and 150 μM during incubation. The U87 cells in the study group were treated with ELF-EMFs and

irinotecan. However, the cells in the study group were exposed to a 1-mT magnetic field (50 Hz) for 1 h during incubation (Figure 1). After a 72-h incubation period, an XTT (2, 3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) test was applied in both groups. IC50 (half maximal inhibitory concentration) values of the study were determined using the GraphPad Prism 6 software. Following, the results of the control and exposure groups, a comparison was performed using the SPSS statistical program.

Glioblastoma cell culture

The glioblastoma cell line was cultured in 6-well tissue culture plates at (3×10^5) mL/well in Dulbecco's modified eagle medium, which also contained 10% fetal bovine serum, 100 µg/mL of streptomycin, and 100 U/mL of penicillin. Next, the cells were incubated and humidified in 5% CO_2 at 37 °C. They were then incubated at different concentrations (1, 2, 10, 25, 50, 75, and 150 µg/mL) of irinotecan for another 24 h. Untreated glioblastoma cells with irinotecan were used as the control. Each groups contained 6-replicated samples. At the end of incubation, apoptotic cell death was determined using the XTT method, which was used to evaluate the cytotoxicity.

Cell viability and XTT assay

The XTT was reduced from a soluble, bright orange derivative to a mixture of cellular effectors. This change of color was came about via the breakdown of the positively-charged quaternary tetrazole ring. Then, glioblastoma cells were added to 30 µL of XTT into each of the wells. Incubation than took place in 5% CO_2, for 4 h at 37 °C. Next, the medium was decanted and to this, 1 mL of dimethylsulphoxide (DMSO) (Sigma-Aldrich, St. Louis, MO, USA) was added into each of the wells to ensure that the formazan salts fully dissolved. As a final step, a UV spectrometer was used to measure the concentration at 450 to 690 nm.

ELF-EMF Exposure system

Generation of the electromagnetic field was performed using 2 solenoids, which had a diameter of 25 cm and height of 10 cm, and were connected serially, and each had 400 turns of copper wire. Throughout the exposure, the cells, in 2 groups, comprising the ELF-EMF-treated and control groups, were maintained in plastic chambers that had been specially designed with measurements that comprised 20 cm × 15 cm × 10 cm. Next, water, at a temperature of 37 ± 0.5 °C and taken from a M48K water bath (Elektro-Mag, Turkey), was circulated through the plastic chambers. The intended temperature was attained at 1 h before the field application and was monitored, prior to and throughout the exposure, very carefully to ensure that the temperature remained stable. The experiment was set-up in the laboratory, in a corner that was secluded so that the field sources from other electronic devices could not have any effect on the measurements that were to be taken. The magnetic field was measured as 1 mT, as seen in Figure 1. Measurement of the field intensity was performed at 10-min intervals, and was seen to vary by ±0.05 mT throughout the exposure. For measurement, the Sypris F.W. Bell 5100 series gaussmeter (Sypris Solutions, Inc. Louisville, KY, USA) was used. A 50-Hz, 1mT ELF-EMF was applied for 1 h.

Figure 1. ELF-EMF exposure system

Statistical Analysis

All of the statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). IC50 values were also calculated using dose response curve analysis via this software program.

RESULTS

The results obtained from the XTT analysis indicated that the ELF-EMF significantly reduced susceptibility towards irinotecan in GBM cells ($P < 0.05$). In addition, while the IC50 value was 14.31 µM in the U87 cells treated with only irinotecan, it was 20.51 µM in the same cell group treated both irinotecan and an ELF-EMF (Figure 2).

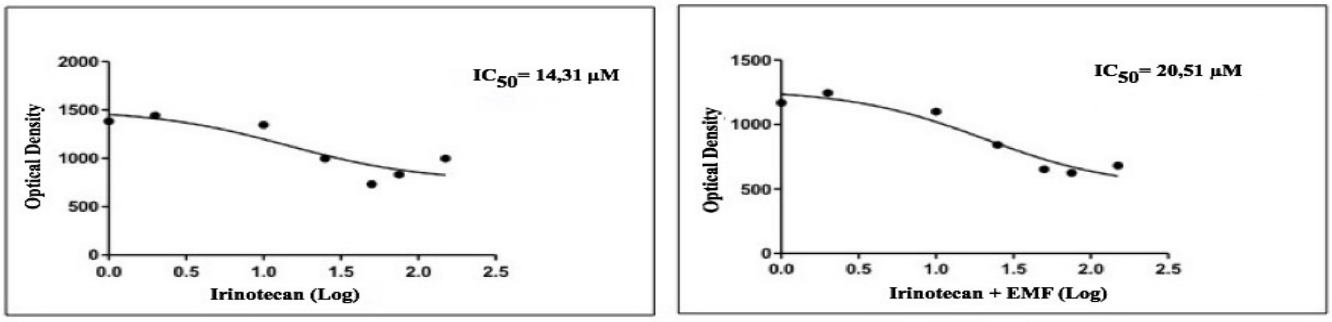

Figure 2. Results of the XTT analysis.

DISCUSSION

The results of this study demonstrated that irinotecan was more efficient alone than the simultaneously applied ELF-EMF and irinotecan in GBM cells. In this preliminary study, it was determined for the first time that an ELF-EMF (50 Hz, 1 mT) could significantly reduce the cytotoxic potential of irinotecan. In actuality, numerous studies have reported that ELF-EMFs affect cancer cells and mechanisms of the drug action.

GBM is the most commonly seen form of malignant and primary brain tumor Despite the multidisciplinary combinations that are used for treatment, the prognosis of patients with GBM is remarkably poor[24]. Irinotecan, which is a topoisomerase I inhibitor, obstructs the religation of DNA double strands and restricts DNA replication, transcription, and repair, thus leading to tumor cell death. Irinotecan, which could cross the BBB, exhibits perfect central nervous system penetration[25]. It is one of the second line drugs for GBM patients. On the other hand, some of the clinical trials have shown that irinotecan treatment can cause various terrible side effects in organisms. These studies encourage the determination of an efficient concomitant agent for both reducing the severe side effects of

irinotecan and increasing its toxic effect on tumor cells[1]. In addition, while irinotecan and similar chemotherapeutic agents are generally more effective when it first given, resistance occurring within the tumor cells following administration is an important barrier to their efficiency. Identifying the factors that influence the sensibility of antineoplastic agents toward cancer cells is important for effective chemotherapy.

The present research was conducted with the aim of investigating the effect that ELF-EMFs had on the cytotoxicity of irinotecan. The results showed that the ELF-EMF (1 mT, 50 Hz) had a non-synergistic effect on irinotecan toxicity in the GBM cells ($P < 0.05$). In other words, the ELF-EMF significantly decreased susceptibility to irinotecan in the GBM cells. As a result, it can be considered that the ELF-EMF reduced the intracellular accumulation of the irinotecan in the GBM cells.

ELF-EMFs have nonsynergistic effects that have been observed in various anticancer drugs in different cancer cells as well. The results of another investigation, similar to that of this study, demonstrated that the administration of carboplatin concomitantly with an ELF-EMF (50 Hz, 7 mT) decreased the efficiency of the carboplatin, which is a chemotherapeutic drug for U-87 cells[21]. This result was in agreement with the results of the current study. However, the synergistic effects of ELF-EMFs have also been reported for many anticancer drugs[18,20]. Numerous factors, which include things like the structure of the drug and the dose administered, they type of cancer cells involved, as well as the ELF-EMF's physical characteristics, can be result in varying synergistic and/or nonsynergistic effects of the ELF-EMF application[18-21]. It was demonstrated that concomitant exposure to an ELF-EMF (100 Hz, 10 mT) and temozolomide enhanced the cytotoxicity of temozolomide in human glioblastoma cells[19]. In another study, it was also reported that ELF-EMF (1.5 mT, 25 Hz) exposure similarly caused an increase in the toxicity of 2 drugs that are used in chemotherapy treatment, namely cisplatin and mitomycin C, in human adenocarcinoma cells in the colon[20]. The observed effects might have resulted because the ELF-EMFs enhanced the cell permeability to these charged drugs as a result of changing the medium conductivity[26].

Moreover, previous studies have demonstrated that ELF-EMFs induce membrane surface charges[27]. EMFs apply an electrical force on the charged drug compounds. This force is able to more effectively push the charged drug molecules through the membrane when compared to passive drug delivery or pure diffusion. It was reported that cell membranes were more permeable to some charged drug molecules because of the flow direction of the electric current[28]. On the other hand, this force can make it difficult for some charged drug molecules to pass through the membrane. These different situations occurred due to direct interaction of the charged drug molecules with the cell membrane after its electric features had been altered by the ELF-EMFs. Hence, changes in the electrical features of the medium caused by the ELF-EMFs may have reduced the ability of the irinotecan to pass into the U87 cells.

Moreover, it was reported that ELF-EMFs may result in the lifetime of superoxides being extended and thus enhance the superoxide concentration in the living cells, increasing the release of free radicals and resulting in genotoxic effects after chronic exposure[29]. Free radicals, which are very reactive, interact with DNA. The activation of p^{53} causes caspase 9 to be activated, which then causes caspase 3 to be activated, which is sufficient to cause death. It is known that free radicals, which are susceptible to mitogen-activated protein kinase, affect several cellular processes, such as cellular differentiation, cell cycle control, and cytokine levels, as well as apoptosis[30]. The results of our study demonstrated that irinotecan alone was far more effective than when it was concomitant an ELF-EMF in the GBM cells. ELF-EMFs with different physical characteristics should be investigated on other standard chemotherapy drugs in future studies in terms of their efficacy, and synergistic

or antagonistic effects. In the event of obtaining similar results with the current study, patients receiving chemotherapy will need to stay away from ELF-EMFs to improve their survival times. Moreover, future investigation would be required to evaluate the in vivo efficacy of ELF-EMFs and determine how ELF-EMFs affect the interaction mechanisms between various cancer cells and chemotherapy drugs.

Magnetic fields place mechanical forces onto particles with magnetic moment and then they have an interaction with the ions that are within the membrane proteins and cations. These forces can cause translation, oscillation, or rotational motion, depending on the mass and mobility of the particle. Thus, the ELF-EMF energy transforms into the kinetic energy of the particle. These interactions play a significant role in the adjustment of the particle's movements and cellular behaviors. In general, the ELF-EMF caused a reduction in the apoptotic effect that the irinotecan had, which possibly occurred as a result of these interaction mechanisms[9,21].

In conclusion, this preliminary study demonstrated that ELF-EMFs reduce irinotecan toxicity in human glioblastoma cells. More comprehensive studies are required that investigate the possible mechanisms clarifying the non-synergistic impact of ELF-EMFs on the cytotoxic capacity of irinotecan, and examine the effects of ELF-EMF on the interaction mechanisms between other chemotherapeutic drugs and cancer cells. Additionally, patients undergoing radiotherapy due to a brain tumor are also advised to take into account the risk of ELFs emitted from the batteries of their mobile phones in terms of irinotecan cytotoxicity until the contradictions on the subject are resolved.

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Ethical Statement: There is no need for an ethics committee decision as the cell line is being studied.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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