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Research Article

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Effects of Electromagnetic Field on Cyclophosphamide-Induced Acute Toxicity and Cancer Progression in Laboratory Mice: A Preliminary Experimental Study

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ABSTRACT

Background: Pulsed electromagnetic field (PEMF) therapy has emerged as a potential adjuvant treatment in oncology, demonstrating selective cytotoxic effects on neoplastic cells while sparing normal tissues. The device, which generates a specific electromagnetic field configuration, has shown promise in preliminary studies. This study aimed to evaluate the effects of exposure on cyclophosphamide-induced acute toxicity and cancer progression in BDF1 hybrid mice.

Methods: Male BDF1 (C57BL/6 × DBA/2) hybrid mice aged 3-4 months were randomized into three groups (n=10 per group): control (cyclophosphamide only, 500 mg/kg i.p.), peripheral zone exposure, and focal zone exposure. Prior to chemotherapy administration, mice in treatment groups received daily exposure (3 hours/day, 3-5 days/week) for three weeks. Mortality rates were monitored for one month following cyclophosphamide injection.

Results: The control group demonstrated 50% mortality consistent with the established LD50 for this strain. Mice exposed to the peripheral zone showed reduced mortality (30%), while those in the focal zone exhibited complete protection with 0% mortality ($p<0.05$). Additional observational studies in tumor-bearing mice demonstrated that exposure significantly improved quality of life indicators, including maintained activity levels and appetite, despite continued tumor progression.

Conclusions: These preliminary findings suggest that electromagnetic field exposure may provide significant protection against cyclophosphamide-induced acute toxicity in a dose- dependent manner related to field intensity. The device shows potential as a supportive intervention during chemotherapy, although it does not appear to inhibit tumor growth directly. Further controlled studies are warranted to elucidate mechanisms and optimize protocols for clinical translation.

Keywords: Pulsed Electromagnetic Field Therapy, Cyclophosphamide, Chemotherapy Toxicity, Mice, Supportive Care, Oncology

Introduction

Cyclophosphamide (CTX) remains one of the most widely utilized alkylating agents in cancer chemotherapy and immunosuppressive therapy [1]. Despite its efficacy against various malignancies, cyclophosphamide administration is associated with significant dose-limiting toxicities, including myelosuppression, immunosuppression, and organ-specific damage affecting the bladder, lungs, and heart [2, 3]. The median lethal dose (LD50) for intraperitoneal administration in mice ranges from 200 to 500 mg/kg depending on strain, with BDF1 hybrid mice demonstrating intermediate sensitivity [4].

Pulsed electromagnetic field (PEMF) therapy has garnered increasing attention as a potential adjuvant treatment modality in oncology [5]. Experimental evidence demonstrates that extremely low-frequency electromagnetic fields can selectively

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inhibit cancer cell proliferation, induce apoptosis, suppress angiogenesis, and enhance the cytotoxic effects of conventional chemotherapeutic agents [6, 7]. Importantly, these effects appear to target malignant cells preferentially while leaving normal cells relatively unaffected.

Furthermore, cyclophosphamide-induced toxicity and electromagnetic field exposure Following a high CP dose (200 mg/kg), low-frequency pulsed EMF exacerbated immunosuppression and bone marrow damage in mice, resulting in decreased spleen weight, a quicker reduction in WBC, and a worse grafting effectiveness of bone marrow cells. Millimeter-wave EMF (42.2 GHz) administered prior to CP did not shield leukocytes, bone marrow cells, or T-cell-mediated immunity from CP toxicity in mice [7]. The authors conclude that PEMF "increases the damage induced in mice by CP," particularly when treated in the first 24 hours post-CP. Sequence dependence is suggested by earlier Soviet research. EMF prior to chemotherapy may offer protection, while EMF following chemotherapy may increase toxicity to leukocytes and bone marrow [8, 9].

The device represents a novel electromagnetic field generator designed to produce a specific field configuration with potential biomedical applications. Preliminary observations have suggested that exposure to the field may influence physiological processes and potentially mitigate certain pathological conditions. However, systematic experimental evaluation of its effects on chemotherapy-induced toxicity has been lacking [10].

In addition, recent research on electromagnetic fields (EMFs) in oncology provides a solid foundation for evaluating innovative devices like the . Several preclinical studies demonstrate that particular EMF exposures can enhance chemotherapy by enhancing tumor cell death and, in some animals, allowing for successful treatment at lower medication doses. Combining low-frequency EMFs (50 Hz, 20 mT) with low-dose doxorubicin significantly increased cytotoxicity in MCF-7 breast cancer cells by increasing reactive oxygen species, inducing G0/G1 cell-cycle arrest, and promoting apoptosis. The combination shifted the doxorubicin IC50 from 2 μM to about 0.25 μM at 24 hours, suggesting a significant dose- sparing potential [11].

Similarly, static magnetic fields (3-24 mT) increased doxorubicin toxicity in G292 osteosarcoma cells, lowering the IC50 from 3.2 μM to 0.8 μM and virtually tripling apoptotic rates. This effect was connected to increased ROS production and disturbance of iron and calcium homeostasis. In osteosarcoma spheroid and monolayer models, properly regulated extremely low-frequency EMFs boosted the efficiency of many chemotherapeutics (cisplatin, methotrexate, ifosfamide, doxorubicin) while sparing mesenchymal cells, emphasizing tumor selectivity. In a rat carcinosarcoma model, combined EMF and doxorubicin treatment inhibited tumor growth and was associated with less hepatic oxidative damage than doxorubicin alone, as indicated by lower lipid peroxidation and serum ALT activity. This suggests that some EMF configurations may mitigate chemotherapy-related organ toxicity [12].

In addition to ELF and static fields, non-thermal radiofrequency and amplitude- modulated radiofrequency exposures have demonstrated pro-apoptotic and antiproliferative effects in a variety of cancer cell lines and animal models, frequently via membrane-level and mitochondrial mechanisms [13]. These effects are being investigated as systemic adjuvants in advanced solid tumors. This evidence suggests that an engineered EMF generator, like the , may influence tumor biology and chemotherapy responses. Further in vivo studies are needed to determine if such fields can improve antitumor efficacy while reducing chemotherapy- induced toxicity in normal tissues [12, 14].

The present study was designed to evaluate the potential of electromagnetic field exposure to modulate acute toxicity induced by cyclophosphamide in BDF1 hybrid mice. Secondary objectives included preliminary observations on the effects of exposure in tumor- bearing animals to assess both anticancer potential and quality-of-life parameters.

Materials and Methods

Figure 1: Workflow for research and experimental design. Three groups of male BDF1 (C57BL/6 × DBA/2) mice were randomly assigned: control (cyclophosphamide only), focal-zone exposure, and peripheral-zone exposure. Before receiving a single intraperitoneal injection of cyclophosphamide (500 mg/kg), animals in treatment groups were exposed to the electromagnetic field every day for three weeks. After chemotherapy, survival and clinical state were tracked for 30 days.

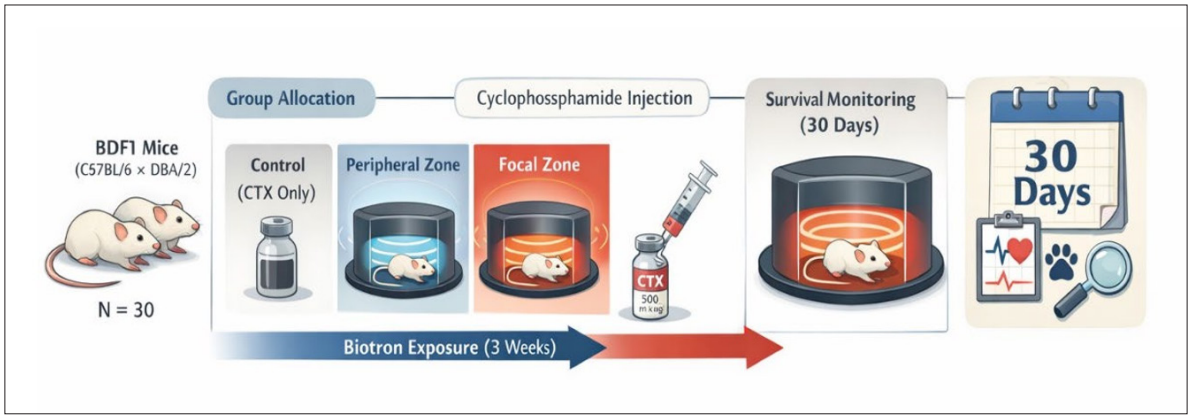

Figure 1: summarizes the entire methodology for this study.

Animals

Male BDF1 hybrid mice (first-generation offspring of C57BL/6 females × DBA/2 males) aged 3-4 months were obtained from the Stolbovaya animal breeding facility. BDF1 mice represent a well-characterized hybrid strain commonly utilized in toxicological and oncological research due to their genetic uniformity and intermediate phenotypic characteristics. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle and ad libitum access to standard rodent chow and water. All experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals.

Device and Exposure Protocol

The device generates a specific electromagnetic field configuration. Two distinct exposure zones were evaluated: the peripheral zone (adjacent to the inner wall of the device) and the focal zone (central region of maximum field intensity). Mice were placed in specialized ventilated plastic mesh containers and positioned in the designated zones during exposure sessions figure 2.

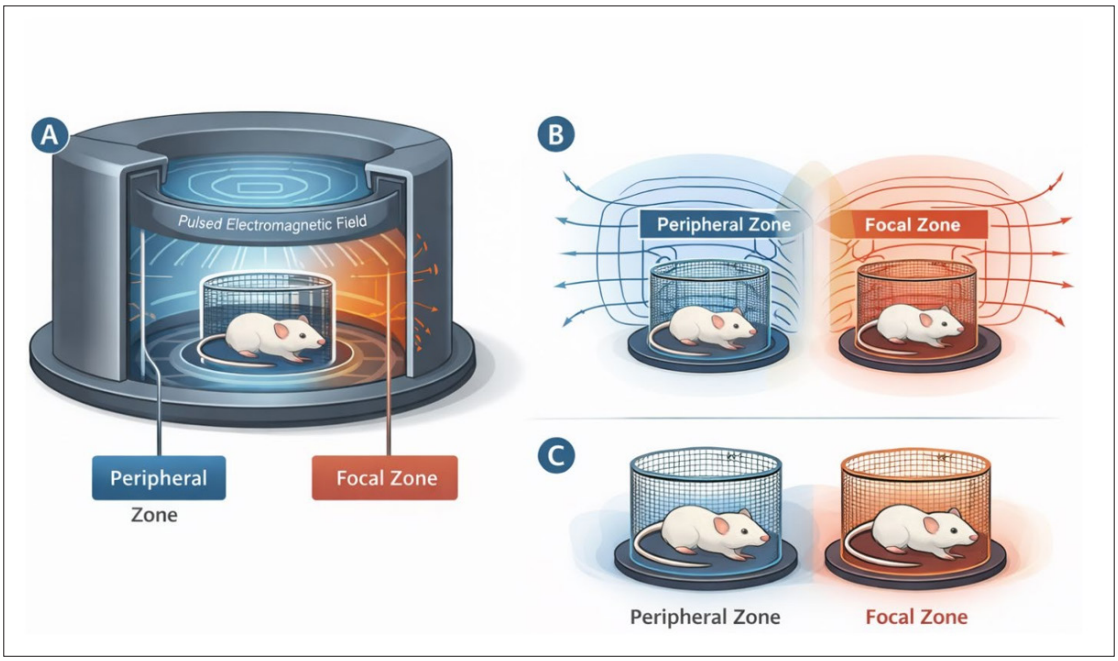

Figure 2: The electromagnetic field generator's peripheral zone (lower field intensity) and focal zone (area of maximum field intensity) are depicted schematically. During exposure sessions, mice were placed in ventilated mesh containers inside the assigned zones. The core area of intense electromagnetic field lines is known as the focus zone.

Experimental Design: Chemotherapy Toxicity Study

Mice were randomly assigned to three experimental groups (n=10 per group): (1) Control group – received cyclophosphamide only; (2) Peripheral zone group – received exposure at the peripheral zone prior to cyclophosphamide; (3) Focal zone group – received exposure at the focal zone prior to cyclophosphamide. The electromagnetic field pre-treatment protocol consisted of daily 3-hour exposure sessions, administered 3-5 days per week for three weeks (October 10 to November 1, 2016). Following the pre-treatment period, all mice received a single intraperitoneal injection of cyclophosphamide (Cyclophosphamide for injection, standard pharmaceutical preparation) at a dose of 500 mg/kg, previously established as the LD50 for this strain and route of administration. Animals were monitored daily for survival and clinical signs for one-month post-injection.

Observational Studies in Tumor-Bearing Mice

Additional observational studies were conducted in mice inoculated with lung carcinoma cells. Animals were divided into control and -treated groups (n=12 per group). The group received daily 2-hour exposures on weekdays. Survival time, tumor size, and behavioral parameters (activity level, food intake, signs of distress) were monitored throughout the study period. A separate long-term study evaluated the effects of regular exposure on naturally occurring age-related cancers in aging mice, with monitoring extended over the animals' lifespans.

Statistical Analysis

Mortality rates were compared between groups using Fisher's exact test. Survival curves were analyzed using the Kaplan-Meier method with log-rank test for group comparisons. A p-value <0.05 was considered statistically significant.

Results

Chemotherapy Toxicity Modulation

The mortality kinetics in the control group (cyclophosphamide only) corresponded to previously established patterns for this mouse strain following intraperitoneal administration of cyclophosphamide at 500 mg/kg. By the end of the one-month observation period, 50% of control animals had succumbed (5 of 10 mice), confirming the LD50 dose level.

In the peripheral zone group, mortality was reduced to 30% (3 of 10 mice), representing a relative reduction of 40% compared to controls. Most notably, mice pre-treated with exposure in the focal zone demonstrated complete protection against lethal toxicity, with 0% mortality (0 of 10 mice) observed throughout the study period ($p<0.05$ vs. control). These findings suggest a dose-response relationship between electromagnetic field intensity and protective effect.

Effects On Tumor-Bearing Mice

In mice bearing transplanted lung carcinoma, all animals in both control and -treated groups eventually succumbed to their malignancies, indicating that exposure does not provide curative anticancer effects. However, notable differences were observed in survival duration and quality-of-life parameters.

Control animals demonstrated a median survival of approximately 3 weeks following tumor inoculation. During the final 10 days, affected mice exhibited typical cancer cachexia syndrome, characterized by marked lethargy, anorexia, and progressive debilitation. In contrast, -treated mice survived approximately 5 weeks, demonstrating maintained activity levels and preserved appetite until the terminal phase. Importantly, while treated animals exhibited prolonged functional status, tumor size at the time of death was somewhat larger than in controls, suggesting the absence of direct anti-tumor effects.

Long-Term Observations in Aging Mice

In the longitudinal study of aging mice, all animals in both groups ultimately died from spontaneous cancers, consistent with the known natural history of laboratory mouse strains. However, treated mice demonstrated significantly delayed cancer mortality, surviving the equivalent of approximately 20 additional human years when extrapolated using standard age conversion factors. As observed in the transplanted tumor model, treated animals maintained functional status and quality of life until near the end of life, with death occurring without the prolonged terminal decline typically observed in control animals.

Blood Parameter Analysis

Collaborative studies conducted at the Institute of Theoretical and Experimental Biophysics (Pushchino, Russia) in tumor-bearing mice (n=11 per group) demonstrated that animals exposed to the focal zone exhibited improved blood parameters compared to controls. On study day 42, when animals were sacrificed for analysis, -treated mice showed superior hematological profiles, consistent with better overall physiological status.

Discussion

The present study provides preliminary evidence that electromagnetic field exposure using the device can significantly modulate cyclophosphamide-induced acute toxicity in mice. The complete protection observed in the focal zone group (0% mortality vs. 50% in controls) represents a substantial effect that warrants further investigation to elucidate underlying mechanisms.

Several mechanisms may account for the observed protective effects. Electromagnetic field therapy has been shown to enhance cellular antioxidant defenses, modulate inflammatory responses, and promote tissue repair mechanisms [15,16]. These effects could potentially mitigate the oxidative stress and inflammatory cascade initiated by cyclophosphamide metabolites, particularly the toxic metabolite acrolein [17]. Additionally, electromagnetic fields may influence cellular membrane permeability and ion channel function, potentially affecting drug distribution and cellular uptake [18].

The dose-response relationship observed between field intensity (peripheral vs. focal zone) and protective effect suggests that the electromagnetic field parameters are critical determinants of biological response. This finding aligns with the broader PEMF literature indicating that specific frequency, intensity, and exposure duration parameters are necessary to achieve therapeutic effects [19].

The observations in tumor-bearing mice present a complex picture with important clinical implications. While exposure did not cure cancer or arrest tumor progression, it substantially improved quality of life and modestly extended survival. The maintained functional status (activity, appetite) despite continued disease progression suggests that the device may exert systemic supportive effects independent of direct anti-tumor activity. Similar dissociations between symptom burden and disease status have been reported with certain palliative interventions [19, 20].

These findings carry an important clinical caveat. The symptomatic improvement observed with treatment could potentially mask disease progression, leading to delayed medical evaluation or false reassurance regarding disease status. In any clinical application, this consideration would necessitate strict adherence to scheduled surveillance protocols independent of symptomatic status.

The remarkable case of the aged mouse treated with intensive exposure during terminal cancer, which survived an additional 40 days (equivalent to approximately 5 human years) with maintained quality of life, suggests potential applications in hospice or palliative care settings for patients with no remaining curative options. However, this represents a single observation requiring systematic validation.

Several limitations of this study must be acknowledged. The sample sizes were relatively small, limiting statistical power for some comparisons. The electromagnetic field parameters of the device were not fully characterized, hampering comparability with other PEMF systems. Additionally, the mechanisms underlying the observed effects remain speculative and require investigation at the molecular and cellular levels.

Future studies should include larger cohorts, detailed characterization of the electromagnetic field parameters, mechanistic investigations including biomarker analysis, and evaluation of effects on standard chemotherapy efficacy to ensure that protective effects do not compromise anti-tumor activity.

Conclusions

This preliminary experimental study demonstrates that electromagnetic field exposure provides significant protection against cyclophosphamide-induced acute toxicity in mice, with effects proportional to field intensity. While the device does not exhibit direct anti-tumor effects, it appears to improve quality of life in cancer-bearing animals. These findings support further investigation of therapy as a potential supportive intervention during cancer chemotherapy, with emphasis on determining mechanisms of action and ensuring maintenance of chemotherapeutic efficacy. Clinical translation would require careful attention to maintaining appropriate surveillance schedules to avoid masking of disease progression.

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