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Cytotoxicity and Genotoxicity Assessment of Gadoteric Acid in Breast Cancer Cells

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Abstract

Background: Gadoteric acid is utilized in magnetic resonance imaging (MRI) as a paramagnetic macrocyclic gadolinium-based contrast agent (GBCA) in breast cancer patients. However, in parallel with its diagnostic and prognostic use, the effect of gadoteric acid on MCF-7 cells has not yet been demonstrated. The aim of this study was to examine the cytogenotoxic effects of gadoteric acid on MCF-7 breast cancer cells.

Methods: MCF-7 cells were incubated with gadoteric acid (0.1-100 mM). The cytotoxic effect was examined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The DNA damage effect of gadoteric acid on breast cancer cells by incubation at multiples of IC_{50} (1.84 mM, 3.67 mM, 7.35 mM, and 14.7 mM) was examined by Comet assay.

Results: Gadoteric acid (1-100 mM) significantly increased cytotoxicity in MCF-7 breast cancer cells ($p < 0.001$, $p < 0.0001$, and $p < 0.0001$, respectively). Gadoteric acid (1.84 mM, 3.67 mM, 7.35 mM, and 14.7 mM) dramatically increased genotoxicity in breast cancer cells ($p < 0.01$, $p < 0.01$, $p < 0.01$ and $p < 0.01$, respectively).

Conclusion: The results of our study indicate that gadoteric acid, which is used for diagnostic purposes in breast cancer, shows cytogenotoxic effect in MCF-7 cells under in vitro conditions. Our findings constitute the basic stepping stone for further studies in terms of therapeutic potential and additional studies are needed for clinical relevance.

Keywords: MCF-7 cell; Gadoteric acid; Cytotoxicity; Genotoxicity; Breast cancer

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Gadoterik Asidin Meme Kanseri Hücrelerinde Sitotoksisite ve Genotoksisite Değerlendirmesi

Öz

Giriş: Gadoterik asit, meme kanseri hastalarında paramanyetik makrosiklik gadolinyum bazlı kontrast madde (GBKA) olarak manyetik rezonans görüntülemede (MRG) kullanılmaktadır. Ancak, tanısal ve prognostik kullanımına paralel olarak, gadoterik asidin MCF-7 hücreleri üzerindeki etkisi henüz gösterilmemiştir. Bu çalışmanın amacı, gadoterik asidin MCF-7 meme kanseri hücreleri üzerindeki sitogenotoksik etkilerini incelemektir.

Yöntemler: MCF-7 hücreleri gadoterik asit (0.1-100 mM) ile inkübe edilmiştir. Sitotoksik etki 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) testi ile incelenmiştir. Gadoterik asidin meme kanseri hücreleri üzerindeki DNA hasarı etkisi IC_{50}'nin katlarında (1.84 mM, 3.67 mM, 7.35 mM ve 14.7 mM) inkübasyon ile Comet testi ile incelenmiştir.

Bulgular: Gadoterik asit (1-100 mM) MCF-7 meme kanseri hücrelerinde sitotoksisiteyi önemli ölçüde artırmıştır (sırasıyla $p < 0.001$, $p < 0.0001$ ve $p < 0.0001$). Gadoterik asit (1.84 mM, 3.67 mM, 7.35 mM ve 14.7 mM) meme kanseri hücrelerinde genotoksisiteyi önemli ölçüde artırmıştır (sırasıyla $p < 0.01$, $p < 0.01$, $p < 0.01$ ve $p < 0.01$).

Sonuç: Çalışmamızın sonuçları, meme kanserinde tanı amaçlı kullanılan gadoterik asidin in vitro koşullarda MCF-7 hücrelerinde sitogenotoksik etki gösterdiğini ortaya koymaktadır. Bulgularımız terapötik potansiyel açısından ileri çalışmalar için temel basamak teşkil etmekte olup klinik uygunluk için ek çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: MCF-7 hücresi; Gadoterik asit; Sitotoksisite; Genotoksisite; Meme kanseri.

INTRODUCTION

Breast cancer is the most frequent malignant tumor in females globally and is the leading cause of cancer death in females[1]. The current treatments include surgery, radiotherapy, chemotherapy, hormonal therapy and immunotherapies[2]. However, the side effects of these treatments such as systemic toxicity and neuropathy, drug resistance and serious deterioration in quality of life due to treatments limit the available treatments[3]. Therefore, new treatment strategies and therapeutic targets continue to be explored and developed[4]. Recently, compounds used for different purposes other than new pharmacological treatments have attracted attention. In this context, research with gadolinium-based contrast agents (GBCAs) is considered important[5].

Gadoteric acid is a GBCAs used in whole-body magnetic resonance imaging (MRI), particularly in breast cancer[6]. In recent years, gadoteric acid has shown cytotoxic and genotoxic effects in different cell types[7], suggesting that it may also exert these toxic effects in breast cancer cells and offer a therapeutic effect beyond diagnostic purposes. Moreover, the fact that other GBCAs show toxic effects on cancer cells in different cancer types reinforces this hypothesis[5]. The fact that gadoteric acid in the macrocyclic class provides more stability and has a safer profile than GBCAs in the linner class increases the necessity of its use in cancer research[8]. In addition, Gd^{+3} ion has recently come to the forefront in theranostics used for both diagnostic and therapeutic purposes, which are promising in cancer treatment[9]. The high clinical utilization of gadoteric acid in breast imaging provides justification for investigating its therapeutic potential in cancer treatment. However, more knowledge about the effects of gadoteric acid on breast cancer cells is needed.

MCF-7 is a breast cancer cell line that has been extensively utilized in many studies for more than 40 years[10]. The identification of agents that increase cytotoxicity in this cell line is indicative of therapeutic potential for breast cancer[11]. As

in many pathological conditions, breast cancer is characterized by dysregulated and malfunctioning apoptotic mechanisms[12]. Gadoteric acid on the other hand has been shown to activate apoptosis. The therapeutic potential of cytotoxic agents by targeting dysregulated apoptosis in breast cancer and the ability of gadoteric acid to induce apoptosis indicate the potential suitability of gadoteric acid for breast cancer research. Furthermore, the cytotoxic effect of GBCAs in other cell lines justifies the evaluation of the cytotoxicity of gadoteric acid in MCF-7 cells.

Recent studies have shown that GBCAs have genotoxic effects in different cell lines[13]. Inhibition of DNA repair or agents that cause DNA damage in breast cancer cells are considered as promising approaches[14]. The genotoxic effect of GBCAs on breast cancer cells remains a scientific gap. Understanding the genotoxic effects of gadoteric acid in MCF-7 breast cancer cells may lead to the development of new strategies for the treatment of breast cancer and improve current therapeutic modalities. It is also thought that gadoteric acid, a contrast agent, may provide new foundations for the therapeutic potential of targeted therapy applications. It needs to be further investigated as an alternative to current treatment methods, especially in common tumors such as breast cancer.

In the clinical field, there are limitations in determining the effect of gadoteric acid on cytotoxicity and genotoxicity in breast cancer patients. Therefore, the cytogenotoxic effect of gadoteric acid in MCF-7 cell line under in vitro conditions can be examined. Investigation of the cytotoxicity and genotoxicity effects of gadoteric acid in MCF-7 cell line may constitute a new step in breast cancer treatment and enlighten the existing literature.

The aim of this study was to investigate the effects of gadoteric acid, one of the GBCAs, on cytotoxicity and DNA damage in MCF-7 breast cancer cell line.

METHODS

Ethical Considerations

We performed in vitro experiments with the commercially available MCF-7 breast cancer cell line. Since primary tissue samples, human participants and/or animal subjects were not used in our research process, ethical approval from any ethics committee is not required. MCF-7 cells were sourced from the American Type Culture Collection (ATCC, Shanghai, China).

Cell culture

Cells were preserved in Dulbecco's Modified Eagle Medium (DMEM) containing glutamine supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Cells were grown at 37°C in a humidified medium with 5% CO_2.

Measurement of cytotoxic effect

To evaluate the cytotoxic effect, cell viability was demonstrated using trypan blue at 0.4% concentration and cell viability was expected to reach 90% as the threshold to start experiments. MCF-7 cells were counted using a Neubauer Improved Hemocytometer (Marienfeld-Superior, Lauda-Königshofen, Germany) under an Olympus CKX53 Inverted Microscope (Olympus Corporation, Tokyo, Japan). Cells were placed in 96-well plates at a concentration of 5×10^4 cells per well to perform 3-(4,5-dimethylthiazol-2-yl)-diphenyl tetrazolium bromide (MTT) assays[15]. MTT reagent was dissolved in Dimethyl sulfoxide (DMSO). Groups were designated on the plate: control, solvent (sterile distilled water) and varying concentrations of Gadoteric acid (0.1-100 mM). These concentration values were used based on previous in vitro studies in the literature[16] and because it is believed that gadoteric acid application in cellular studies is within safe limits at these concentration values[17]. In the gadoteric acid groups, breast

cancer cells were exposed to gadoteric acid at concentrations of 0.1-100 mM for 24 hours. The cytotoxic effect of gadoteric acid was evaluated by measuring the percentage of cell viability. In addition, the IC_{50} value was calculated by GraphPad Prism version 9.0.0. IC_{50} concentration value was determined as 7.35 mM from these results.

Evaluation of genotoxic effect

The Comet experiment was conducted using the protocol developed by Singh et al[18] with slight changes. Cells were placed in eppendorf tubes containing 5×10^5 cells. Gadoteric acid (in 100 µl) was added to the tubes at concentrations of IC_{50} (7.35 mM), about a quarter (1.84 mM), half (3.67 mM) and twice (14.7 mM) the IC_{50} rating. After centrifugation and incubation, the supernatant was thrown away. The residual cell pellet was treated with phosphate buffered saline (PBS) and low melting point agar (LMA) and spread on microscope slides and sealed with coverslips. The slides were then mounted in a container with lysis solution. Refrigerated for 1-16 hours and the process was completed the next day. Before electrophoresis, the slides were placed in an electrophoresis chamber in alkaline buffer. Electrophoresis was then activated at 25 V (300 mA) for 20 minutes. After this, the slides were neutralized and stained with SYBR Green I (1:10,000 dilution in TE buffer).

For each group, a sample of 100 cells was selected and analyzed. Cells were quantified according to the degree of nuclear damage.

Level 0 = Not disturbed, Level 1 = Slightly disturbed, Level 2 = Moderately disturbed, Level 3 = Severely disturbed, Level 4 = Very severely disturbed.

Number of Level 0 cells (D0) × 0

Number of Level 1 cells (D1) × 1

Number of Level 2 cells (D2) × 2

Number of Level 3 cells (D3) × 3

Number of Level 4 cells (D4) × 4

N = Total number of cells (100)

Genetic Damage Index (GDI)=(0×D0 + 1×D1 + 1×D1 + 2×D2 + 3×D3 + 4×D4)/N

The sum of the average amount of damaged cells (Level 2, Level 3 and Level 4) expressed as the damaged cell index (DCI)[19].

Statistical Analysis

We carried out statistical analyses with GraphPad Prism version 9.0.0 for Windows. Cytotoxicity, GDI and DCI levels were evaluated by one-way analysis of variance (ANOVA) and Tukey's multiple comparison test. Values are expressed as mean ± SD. Comparisons were defined as statistically significance when $p < 0.05$. The significance values are shown in the figures as below: ** = $p < 0.01$, *** = $p < 0.001$ and **** = $p < 0.0001$.

RESULTS

Gadoteric acid displays cytotoxic effect in MCF-7 cells

There was no difference in cell viability in MCF-7 cells between solvent and control ($p > 0.05$). No statistically significant change was observed between gadoteric acid (0.1 mM) and the control group in terms of cell viability value in breast cancer cells ($p > 0.05$). Gadoteric acid (1 mM) significantly lowered cell viability in MCF-7 cells relative to control (Figure 1A; $p < 0.001$). Gadoteric acid (10 mM) enhanced the degree of cytotoxicity in MCF-7 cells relative to the control (Figure 1A; $p < 0.0001$). Gadoteric acid (100 mM) was also significantly enhanced in degree of cytotoxicity as relative to control (Figure 1A; $p < 0.0001$). The cytotoxic action of gadoteric acid appeared to be dose-dependent. The effect of gadoteric acid on cell viability was measured as $LogIC_{50} = 0.866$, equivalent to an IC_{50} value of 7.35 mM (Figure 1B).

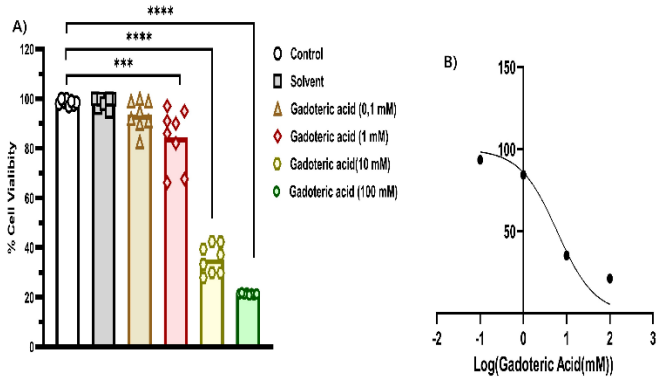

Figure 1. A) Effect of gadoteric acid (0,1-100 mM) on cell viability in MCF-7 cells. ***P < 0.001 or ****P < 0.0001 vs control (one-way ANOVA, post-test Tukey). **B)** LogIC_{50} dose-response curve for varying Gadoteric acid concentrations (0,1-100 mM).

The genotoxic potential of gadoteric acid in MCF-7 cells

GDI and DCI values indicate genotoxicity in comet assay test. Gadoteric acid (1.84 mM) demonstrated a statistically significant elevation in GDI as relative to control (Figure 2; $p < 0.01$). Gadoteric acid (3.67 mM) also resulted in a statistically significant elevation in GDI relative to the control (Figure 2; $p < 0.01$). Exposure to gadoteric acid at IC_{50} also caused a statistically significant elevation in GDI relative to control (Figure 2; $p < 0.01$). Gadoteric acid (14.7 mM) had significantly enhanced genotoxicity in MCF-7 cells relative to control (Figure 2; $p < 0.01$).

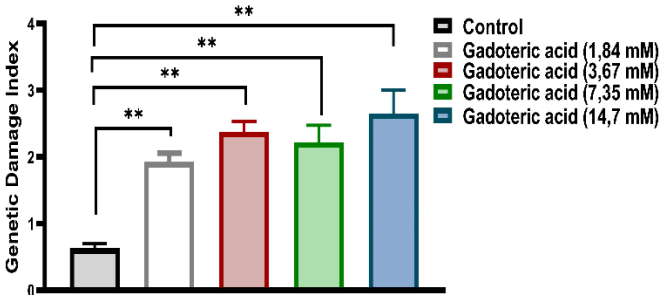

Figure 2. Mean ± SD values of GDI of gadoteric acid (1.84 mM, 3.67 mM, 7.35 mM and 14.7 mM) in MCF-7 breast cancer cells **P < 0.01 (one-way ANOVA, post-test Tukey) versus control.

Gadoteric acid (1.84 mM) resulted in a statistically significant elevation in DCI in MCF-7 cells as relative to control (Figure 3; $p < 0.01$). Gadoteric acid (3.67 mM) also caused a statistically significant elevation in DCI as relative to control (Figure 3; $p < 0.01$). Exposure to gadoteric acid at IC_{50} also significantly increased the DCI as relative to control (Figure 3; $p < 0.01$). Gadoteric acid (14.7 mM) displayed a statistically significant elevation in DCI value as relative to control (Figure 3; $p < 0.001$). The genotoxic effect of gadoteric acid in MCF-7 cells was dose-dependent.

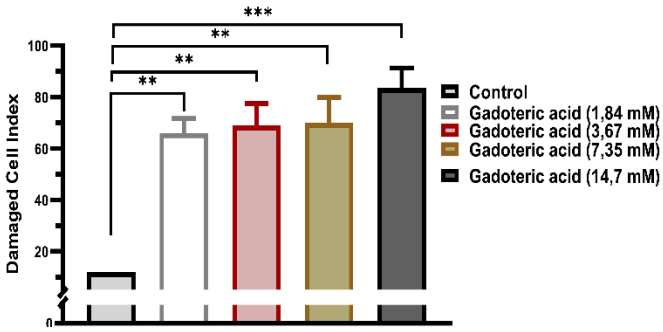

Figure 3. Mean ± SD values of DCI of gadoteric acid (1.84 mM, 3.67 mM, 7.35 mM and 14.7 mM) in MCF-7 cells **P < 0.01 or ***P < 0.001 (one-way ANOVA, post-test Tukey) versus control.

Representative DNA damage images of gadoteric acid (1.84, 3.67, 7.35, and 14.7 mM) application in MCF-7 cells are displayed in Figure 4.

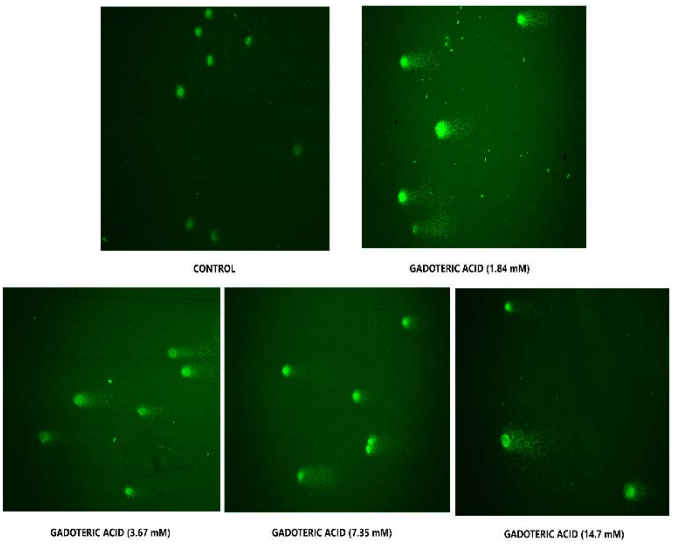

Figure 4. Representative DNA damage images of gadoteric acid (1.84, 3.67, 7.35, and 14.7 mM) administration in MCF-7 cells.

DISCUSSION

The findings of our study indicate that gadoteric acid, which is used for imaging in breast cancer patients, has a cytotoxic effect on MCF-7 cells. IC_{50} value was determined in the cytotoxic effect of gadoteric acid in MCF-7 cell line. In addition, gadoteric acid showed genotoxic effect and caused DNA damage in MCF-7 cells. These results suggest that gadoteric acid may have potential biological activity besides its diagnostic use and that further studies on its possible therapeutic effects are warranted.

While GBCAs have been used for diagnostic purposes, their safety has recently been called into question because they cause gadolinium ion retention and accumulation in tissues [20]. This retention and accumulation has been shown to cause cytotoxicity in cells through inflammation, oxidative stress, and apoptosis[7]. However, there is little information in the literature about its use in cancer treatment. In the study by Supawat et al. it was determined that GBCAs decreased cell viability in K562 cancer cells[21]. The outcomes of this study are compatible with the cytotoxic effect of gadoteric acid, one of the GBCAs, on the MCF-7 cell line. However, long-term application of gadopentetic acid and gadodiamide, which are GBCAs, increased the expression of TRPC5, an indicator of chemotherapeutic drug resistance, in MCF-7 and SK-BR-3 cell lines[22]. The partial contradiction with our study may be due to the exposure to chemotherapeutic agents, the difference in the duration of application and the difference in the GBCAs applied. Apart from that, in our study, the effect of gadoteric acid in reducing cell viability in breast cancer cells is dose-dependent. Our finding of a dose-dependent increase in cytotoxicity can be explained by the fact that the amount of gadolinium retention and accumulation increases with increasing dose.

The effect of GBCAs on genotoxicity in various cell types is still under debate[23]. It has been reported that gadoversatamide increases genotoxicity in human lymphocytes while gadoteric acid does not alter genotoxicity[24]. The gadoteric acid doses used in this study ranged from 1 to 25 mM, which is close to the concentration values used in our study. However, in our study, gadoteric acid increased genotoxicity in MCF-7 cells. These differing results may be due to the differences in the cell line and method used. In this study, the micronucleus test was used to evaluate healthy lymphocyte cells, while in our study, the comet assay was used to evaluate cancer cell lines. These results can be speculated to increase genotoxicity in cancer cells without causing DNA damage in healthy cells. This may indicate its therapeutic potential in breast cancer patients without a side effect profile. Gadolinium has also been shown to cause DNA damage in glioblastoma cells by increasing platinum accumulation[25]. This evidence is in line with our results that gadoteric acid increased DNA damage in MCF-7 cells.

As in other types of cancer, chemotherapy is also used in breast cancer[26]. One of the mechanisms of action of these treatments is the inhibition of DNA replication in cancer cells and the generation of reactive oxygen species (ROS) that can cause cytotoxicity and genotoxicity in cancer cells[27]. However, the serious side effects of these chemotherapy drugs point to the need to develop new treatment options. Therefore, it is important to evaluate new agents with a low side effect profile that may increase ROS production in breast cancer treatment[28]. Gadoteric acid has been shown to induce ROS increase in different tissues causing oxidative stress[29]. In addition, gadoteric acid has the ability to show cytotoxic and genotoxic effects in different cells through oxidative stress[30]. The fact that gadoteric acid causes cytogenotoxicity in MCF-7 breast cancer cells may suggest that oxidative stress may be the underlying mechanism.

Limitation

Our study has important limitations. First, the exposure of gadoteric acid in MCF-7 cells in our study was of short duration. In addition, since it is an in vitro study, the real clinical relevance of our data is not clear, which is also one of the important limitations. However, although in vitro studies are not as high in the hierarchy of evidence as clinical studies, they have a place in the hierarchy of evidence. The lack of integration of in vivo, in silico and/or clinical studies is a deficiency as the study only progressed in vitro. Another limitation is the lack of mechanistic investigations in which oxidative stress and/or inflammation may be involved in the cytogenotoxic effects of gadoteric acid. Another limitation is the use of a single cell line, MCF-7 cells, as a breast cancer cell line. This limits generalizability for breast cancer subtypes. Further studies using other breast cancer cell lines (e.g. MDA-MB-231, SK-BR-3, BT-474) may strengthen the findings. Furthermore, the cytogenotoxic effect of gadoteric acid has only been evaluated in cancer cell lines. The fact that the cytotoxic and genotoxic effects of gadoteric acid have not been evaluated in healthy human cell lines (e.g., fibroblasts or epithelial cells) limits our ability to investigate its specificity for cancer cells and its therapeutic window potential. To fully elucidate the translational value of the findings, it is recommended that future studies include experiments using healthy cell lines. In addition, the administration of gadoteric acid in the form in which it is in clinical use may not be due to the effects of the chemical component alone. The in vitro concentration values used in this study do not directly translate to clinical applicability. Since pharmacokinetic factors such as protein binding and tissue distribution cannot be captured in a monolayer culture environment, the human equivalent dose (HED) cannot be calculated, and therefore there are limitations in directly translating this to the clinical setting. Translational studies such as pharmacokinetics and toxicity profile should be conducted to translate the in vitro findings of this study to the clinical field. In addition, another limitation of our study is that our IC_{50} value of 7.35 mM is very high compared to chemotherapy candidate studies.

The results of this study demonstrate for the first time that gadoteric acid decreases cell viability in MCF-7 cells. Furthermore, gadoteric acid also caused DNA damage in breast cancer cells. Our finding of cytogenotoxic effect of gadoteric acid on breast cancer cell line needs additional preclinical and clinical studies.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Committee Approval: We performed in vitro experiments with the commercially available MCF-7 breast cancer cell line. Since primary tissue samples, human participants and/or animal subjects were not used in our research process, ethical approval from any ethics committee is not required. MCF-7 cells were sourced from the American Type Culture Collection (ATCC, Shanghai, China).

Conflict of Interest: The authors declared no conflicts of interest.

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