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Research Article

Cell death induced by a non-selective calcium channel blocker (Fendiline) in colorectal and breast cancer cells

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ABSTRACT

Background: Breast and colorectal cancer are two leading malignancies. Potential cytotoxic effects of available chemotherapies against these cancers need to be explored. Fendiline is a calcium channel blocker and has shown anticancer potential against cancers. By using the *in vitro* approach, we studied the toxicity profile of fendiline against breast and colorectal cancer.

Methods: Cancer cell lines for breast (MDA-MB-231 and MCF-7) and colorectal (SW480, SW620, Caco-2) were cultured and exposed to fendiline (0.75-100µM) for three-time intervals (24-72h). Resulting toxic effects were explored by using a dye reduction assay and were compared as percentages of untreated controls.

Results: All the selected cancer cell lines showed comparable toxic profile of fendiline (IC50: 5.9-9.3µM, 72h). The cell lines demonstrated a steep decline in the growth curve at concentrations higher than 6.25µM. The toxic effects were concentration and time dependent in all five cell lines representing the breast and colorectal cancer.

Conclusion: Fendiline holds a very promising cytotoxicity profile against breast and colorectal cancer. Provided with further studies, the drug can be used against the two malignancies in clinical scenarios.

Key Words: Chemotherapy, Fendiline, Toxic profile, Cancers

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, with colorectal cancer and breast cancer are among the most common and lethal types of cancer [1]. As per World Health Organization (WHO) data, colorectal cancer covers approximately 10% of all reported cancer cases world-wide, while breast cancer is the most frequently found cancer among women population, accounting for almost 25% of all the new cancer cases [2, 3]. Despite significant advancements for early detection, surgical strategies, and chemotherapeutic options, prognosis of the patients with advanced stage of cancers remains poor [4]. This fact highlights urgent need to identify novel therapeutic options to target cancers. Colorectal cancer primarily affects the colon and rectum and is often presented with advanced stage due to its underline early symptoms [5].

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Patients diagnosed with the metastatic stage of colorectal cancer have a low 5-year survival rate (less than 15%) highlighting failure of the existing treatment options to effectively control metastasis and recurrence [6]. Similarly, breast cancer, often treatable when detected at earlier stage, remains major healthcare challenge, especially in advanced metastatic phases [7]. The two cancers demonstrate substantial cellular heterogeneity which lead to varied responses towards the therapies. Therefore, exploring new avenues that could target fundamentals of these common cancers is essential to improve patient survival [8].

Considering above context, a promising therapeutic approach is to target intracellular calcium signaling cascades. Calcium ions have a central role in many physiological processes including cellular proliferation, migration, differentiation, apoptosis and invasion. In the non-cancerous cells, calcium mediated signaling is highly regulated via various channels including pumps and exchangers that could control the influx, efflux, and storage of the calcium within cellular environment [9]. However, in transformed cancer cells, the delicate balance is disrupted and leads to the aberrant calcium mediated signaling chains and supports cancerous

propagations such as uncontrolled cell proliferation, survival and metastasis routes [10]. Calcium signaling in cancer cells is often manipulated by the activation and opening of ion channels including voltage-gated calcium channels (VGCCs), transient receptor potential (TRP) and store-operated calcium entry (SOCE) channels. These channels are vital for maintaining the cellular calcium balance and regulating the processes such as apoptosis and cell cycle progression [11]. Interestingly, *in vitro* investigations in cancer cell lines have exhibited altered calcium homeostasis leading to their aggressive behavior. For example, increased influx of extracellular calcium ions has been linked with increased cell division, resistance towards apoptosis and high cell migration; all vital features of metastatic phase [12]. Thus, therapeutic importance of calcium channels has been recognized in cancer research. Considering this, calcium channel blockers, typically used for cardiovascular diseases including hypertension and arrhythmias, have demonstrated promise in inhibiting cancer cell survival. By blocking calcium influx, these agents could reverse deregulated calcium signaling chains that contribute to cancer cell survival and metastasis [13, 14].

Among various calcium channel blockers, fendiline is a non-selective blocker with the promising anticancer properties. Originally developed for cardiovascular benefits, fendiline is now known to inhibit calcium channels including L-type and T-type channels [15]. Non-selectivity of fendiline allows to affect broader range of the cellular processes as compared to the more selective agents. This broader activity may account for potential effectiveness of fendiline in disrupting cancer cell survival while inducing apoptosis in a variety of cancer types [16]. Several preclinical studies have highlighted that fendiline exerts substantial anticancer effects particularly in the cells of solid tumors. These effects are supposed to be due to fendiline's ability to lower intracellular calcium concentrations, while interfering with the critically important signaling pathways responsible for cancer cell survival and migration. In addition, fendiline has been found to potentiate the effects of other antineoplastic agents suggesting its potential as part of combinational therapy approach [17-20]. Although fendiline's effects in cardiovascular domain are well documented, its anticancer effects and associated mechanisms are not understood well. The data show that fendiline disrupts calcium-dependent signaling pathways controlling cell growth and apoptosis. Reduced intracellular calcium may alter the pathways leading to cell cycle arrest and/or apoptosis, which could be the reasons behind the observed decrease in cancer cell proliferation following fendiline exposure. Additionally, ability of fendiline to halt cell migration and invasion suggests its potential to reduce the metastasis, a major challenge and cause of death in cancer patients [21-23].

Current study was designed to find the toxic effects of fendiline exposure on primary and metastatic breast and colorectal cancer cells. This *in vitro* study highlighted the cell death capacity of fendiline against these cancer cells.

METHODS

Compounds

Chemicals used in the study were purchased from a commercial company. Fendiline (J63254.06), cell culture medium RPMI-1640 (21875-034), FBS (10270-106), antibiotics (15140-122) and L-glutamine (A2916801) were purchased from ThermoFisher Scientific.

Cell Culture

Human cancer cell lines were obtained from American Type Culture Collection (ATCC) previously. For the study, three colorectal cancer cell lines (SW480, SW620, Caco-2) and two breast cancer cell lines (MDA-MB-231, MCF-7) were cultured while using the recommended medium and culture conditions.

Cell Death Assay

Fendiline was dissolved in 1X PBS, and the stock solution was used to treat the cultured cell lines. The experiments were carried out by using cell culture plates (96-well), where cell lines were cultured (3000-4000 cells/well) and exposed with fendiline different concentrations i.e., 0.75-100µM. The exposure was given for 24, 48 and 72h. After exposure period, a cell penetrating compound (MTT) was loaded, allowed to enter the cells and converted into purple color crystals by the mitochondrial enzymes produced from viable cells. The crystals were dissolved by using an organic solvent (DMSO) and coloration was assessed numerically by using ELISA reader. The values were used to plot graphs by means of GraphPad Prism software.

Statistical Analysis

The cell proliferation was shown as numerical values and percentages as compared to untreated control samples. Inhibitory concentrations, defined as values that reduce specific biological activity by a specific percentage, were determined by GraphPad Prism software v10.3.

RESULTS

Cancer Cell Death by Fendiline in Colorectal Cancer Cells

Fendiline, a known chemotherapy, was tested to impose cell death in three colorectal cancer cell lines. Exposure with fendiline induced a sharp cell death as shown in Figure 1. After fendiline exposure, there was inhibition of cell proliferation. This phenomenon was noticeable in all three colorectal cancer cell lines. At high concentrations (≥3.12μM), cell death was clear in the colorectal cancer cell lines. Importantly, the cell lines showed a sharp decrease in proliferation after exposure to fendiline higher concentrations (≥12.5μM). In addition, toxic effects of the compound were observed in all three colorectal cancer cell lines and were comparable with each other. These growth inhibitory effects were also time and concentration dependent. This shows high level of cell death after high concentration of fendiline over longer exposure period. Inhibitory concentration (ICs) are shown in Table 1.

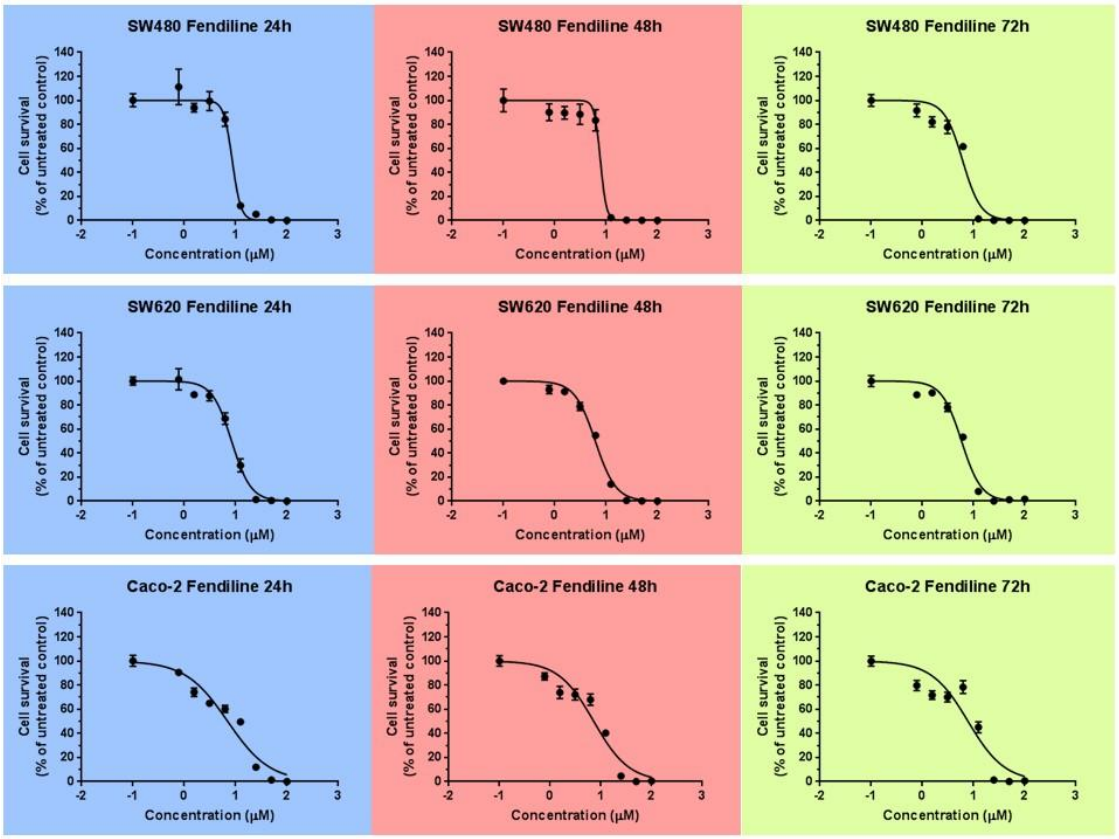

Figure 1: Colorectal cancer cells growth inhibition by fendiline. Exposure with the drug-imposed cell death in three colorectal cancer cell lines, which was measured by using MTT dye reduction assay. The survival curves were generated by using colorimetric readings and GraphPad Prism software.

Table 1: Inhibitory concentrations (ICs) of fendiline against colorectal cancer cell lines identified by MTT assay and GraphPad Prism v.10.3 software.

	Colorectal Cell Lines		
	SW480	**SW620**	**Caco-2**
24h	IC25: 6.9μM IC50: 8.6μM IC75: 10.7μM	IC25: 5.2μM IC50: 8.4μM IC75: 13.1μM	IC25: 2.5μM IC50: 7.1μM IC75: 19.4μM
48h	IC25: 6.6μM IC50: 7.7μM IC75: 9.1μM	IC25: 3.7μM IC50: 6.2μM IC75: 10.2μM	IC25: 3.1μM IC50: 7.3μM IC75: 17.4μM
72h	IC25: 3.9μM IC50: 6.1μM IC75: 9.6μM	IC25: 3.5μM IC50: 5.9μM IC75: 9.5μM	IC25: 3.1μM IC50: 7.8μM IC75: 19.1μM

Cancer Cell Death by Fendiline in Breast Cancer Cells

Breast cancer cell lines were exposed to fendiline and resulting cell death was measured. The drug induced toxic effects in both breast cancer cell lines as shown in Figure 2. As observed in colorectal cancer cells, lower concentration of fendiline showed negligible effects on cell death in the breast cancer cells. However, at higher concentration (≥3.12μM), there was gradual decrease in cell proliferation. The effects were concentration dependent as high level of cell death was seen with high concentration of fendiline. In similar fashion, inhibition was also time dependent as higher levels of cell death was achieved with the same concentration of drug after 72h. Inhibitory concentrations of the compound shown in Table 2 showed the time and concentration dependent effects of fendiline against breast cancer cell lines.

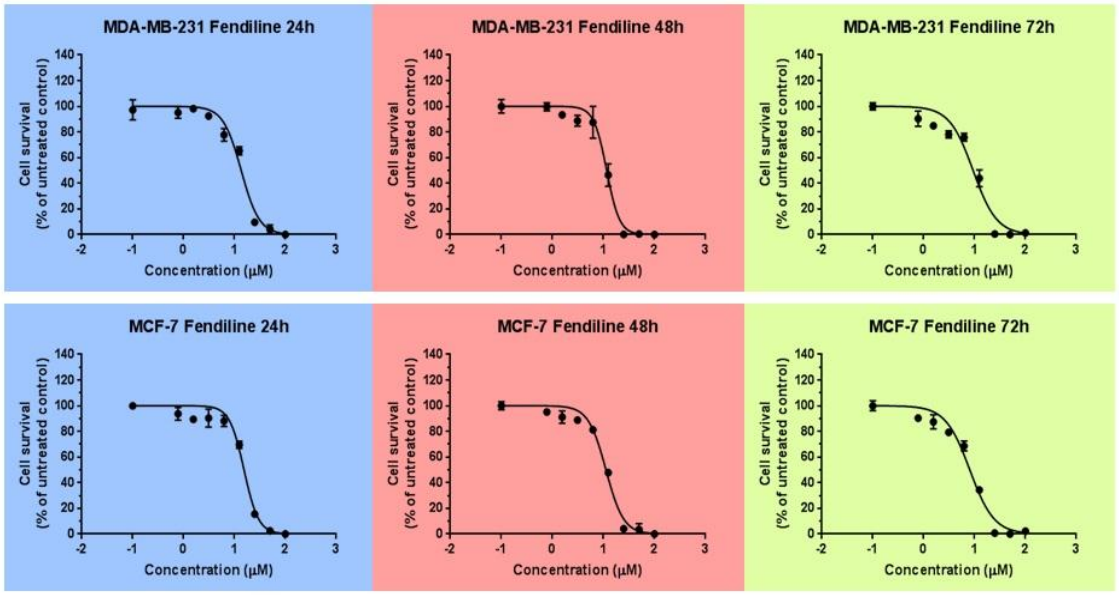

Figure 2: Breast cancer cells growth inhibition by Fendiline. Exposure with Fendiline imposed cell death in the two breast cancer cell lines. The effects were measured by using MTT dye reduction assay and ELISA readers. The survival curves were generated by using colorimetric readings and GraphPad Prism software.

Table 2: Inhibitory concentrations (ICs) of Fendiline against breast cancer cell lines identified by MTT assay and GraphPad Prism v.10.3 software.

	Breast Cell Lines	
	MDA-MB-231	**MCF-7**
24h	IC25: 8.7μM IC50: 13.5μM IC75: 21.3μM	IC25: 10.7μM IC50: 15.1μM IC75: 22.3μM
48h	IC25: 8.3μM IC50: 11.5μM IC75: 15.8μM	IC25: 7.2μM IC50: 11.2μM IC75: 17.3μM
72h	IC25: 5.2μM IC50: 9.3μM IC75: 16.9μM	IC25: 4.4μM IC50: 7.9μM IC75: 14.8μM

DISCUSSION

Chemotherapy is corner stone to manage cancers. There are different categories of chemotherapies available for this purpose. Primally, these compounds interact with cellular partners and induce cytotoxic effects. Despite the associated side-effects, chemotherapeutic drugs hold the central place in cancer treatment. Understanding the functional effects in cancer cells and related molecular mechanisms affected by chemotherapies is crucial to uncovering their full strength [24]. In this study, we used a chemotherapy drug (fendiline) and evaluated its toxic effects against breast and colorectal cancer cells. Fendiline is a non-selective blocker of calcium channel and was originally developed for the management of coronary heart disease [25]. The drug primarily works by blocking the calcium channels and preventing calcium ions from entering the cells. At molecular levels, the drug interacts with multiple signaling cascades including K-Ras pathway. Due to this ability, fendiline gained importance in cancer treatment domain especially for those malignancies where K-Ras network is more prominently involved [26-29].

Breast and colorectal cancers are the most prevalent diseases in the world as per GLOBOCAN 2024 statistics. Heterogeneity of the disease and metastatic potential add to the adverse effects induced by these cancers. Despite availability of multiple treatment options, breast and colorectal cancer control is challenging [30-32]. Novel and existing anticancer medicine need to be assessed for their potential use to control these malignancies. In this study, focus was to highlight the toxic effects of fendiline against breast and colorectal cancer *in vitro* conditions. Negligible literature is available in this domain and needs due attention. For said purpose, we cultured the breast and colorectal cancer cell lines comprising of the primary (SW480, Caco-2, MCF-7) and metastatic (SW620, MDA-MB-231) models. Exposure with a range of fendiline (0.75-100μM) concentration was given for three time points i.e., 24, 48 and 72h. This range of concentration, differ by almost 100fold, was necessary to monitor the cell response. Equally important was the time point selection, as all the selected cell lines are known to complete their respective cell cycle in 22-34h period.

When compared the data from three colorectal cancer cell lines, we noticed that all the three cell lines were least responsive until the applied concentration of 3.12μM. However, at further increased concentration, there was increased toxicity and especially a very steep decline in viable cell number was achieved from 12.5μM concentrations. This steep decline in growth curve was most prominent in SW480 cells, followed by SW620 and Caco-2 (Figure 1). This in turn shows a threshold level of resistance (~6.25μM) and beyond this, the cells responded clearly. Interestingly, the same phenomenon was observed for breast cancer cell lines (Figure 2). Comparable toxicity profile of fendiline was observed in the two breast cancer cell lines, which were different from each other at receptor levels (MDA-MB-231: ER/PR/HER2 negative, MCF-7: ER/PR positive). In addition to this, as shown by Table 1 and 2, the colorectal cancer cell lines were fractionally more responsive towards fendiline exposure with lower IC values as compared to breast cancer. This highlights that cancer cells originating from different tissues with different molecular features and mutation status respond differently towards fendiline exposure. Additionally, dependency level of the cancer cell lines on calcium channels and associated signaling cascades can add further to varied response levels towards fendiline exposure. Time lapses are very important when someone talks about treatment with anticancer compounds. We treated the cancer cell lines for three time periods and observed that fendiline imposed more intense toxicity at later time intervals (72h) as compared to earlier time points (24h). This fact is visible when we compare the IC values of the cells related to early and late time intervals (Table 1 and 2). This information is clinically important as it shows systemic infusion of lower concentrations of fendiline for longer time intervals may lead to better toxic effects with the possibility of lower side-effects.

To conclude, fendiline imposed clear and prominent cytotoxic effects in breast and colorectal cancer cells in concentration and time dependent format. These effects were uniformly imposed in primary and metastatic cancer cells lines, which shows the potential of this drug to control primary as well as advanced stages of the two cancers. Further molecular features associated pathways and *in vivo* assessments are needed to explore this drug against breast and colorectal cancer as a single agent or a part of combinational therapeutic approach.

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