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AZD-1390 Impairs Cell Mobility and Induces ROS-triggered Apoptotic Cell Death in Ovarian Cancer Cell Lines

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Abstract

The Ataxia Telangiectasia mutation (ATM) gene codes for a protein that is a serine/threonine kinase. Phosphorylation of ATM prevents tumor formation by preserving genomic integrity. Somatic mutations in the ATM gene have been identified in some types of ovarian cancer (OC). In this study, we aimed to determine the effects of ATM inhibitor AZD-1390 in ovarian cancer cell lines. Our results showed that AZD-1390 exhibited an antiproliferative effect by decreasing cell viability in ovarian cancer cells in a dose- and time-dependent manner. Further analysis revealed that AZD-1390 significantly inhibited cell migration and increased apoptotic cell death by triggering Reactive Oxygen Species (ROS) activity. Taken together, our findings suggest that ATM inhibition with AZD-1390 is effective in the treatment of ovarian cancer cells. However, further studies are needed to further inform this study.

Keywords

AZD-1390,
ATM,
Ovarian Cancer,
Cell Proliferation

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AZD-1390, Yumurtalık Kanseri Hücre Hatlarında Hücre Hareketliliğini Bozuyor ve ROS Tetiklemeli Apoptotik Hücre Ölümünü İndükliyor

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Özet

Ataksi Telanjiektazi mutasyonu (ATM) geni serin/treonin kinaz için bir protein kodlayan bir gendir. ATM'nin fosforilasyonu, genomik bütünlüğü koruyarak tümör oluşumunu önlemektedir. ATM genindeki somatik mutasyonlar bazı yumurtalık kanseri tiplerinde tespit edilmiştir. Bu çalışmada, AZD-1390 ile ATM inhibitörünün yumurtalık kanseri hücre hatlarında etkilerini belirlemeyi amaçladık. Sonuçlarımız, AZD-1390'ın yumurtalık kanseri hücrelerinde doz ve zamana bağlı bir şekilde hücre canlılığını azaltarak antiproliferatif bir etkiye sahip olduğu belirlenmiştir. Yapılan ileri analizler, AZD-1390'ın Reaktif Oksijen Türleri (ROS) aktivitesini tetikleyerek hücre göçünü önemli ölçüde engellediğini ve apoptotik hücre ölümünü artırdığını ortaya koydu. Bulgularımız bir araya getirildiğinde, AZD-1390 ile ATM inhibisyonunun yumurtalık kanseri hücrelerinin tedavisinde etkili olduğunu göstermektedir. Ancak, bu çalışmayı daha da güçlendirmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler

AZD-1390,
ATM,
Yumurtalık Kanseri,
Hücre Proliferasyonu

1. INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy known worldwide. Approximately 22,000 patients worldwide are diagnosed with ovarian cancer each year, making it the most common type of cancer in women [1]. Furthermore, OC is the fifth leading cause of death among women. Although ovarian cancer is known to be a frequently occurring cancer type worldwide, it is often known to be fatal due to late diagnosis and the emergence of drug resistance [2]. OC poses a significant challenge in modern gynecological oncology in terms of both diagnosis and treatment [3]. OC, often known as the "silent killer," is not diagnosed until it reaches an advanced stage due to its vague symptoms, making it difficult to treat [4]. New treatment strategies are needed to overcome this situation. Recent studies indicate that cancer susceptibility genes, including ATM, CHEK2, and RAD51C, confer differential risks for breast, ovarian, and other cancers. Furthermore, ATM absence or inhibition has been reported to degrade ATM-mediated DNA repair, leading to Homologous Recombination Repair (HRR) deficiency in ovarian cancer cells [5].

Ataxia-telangiectasia (AT) is known as a monogenic, autosomal recessive disease characterized by cerebellar ataxia and oculocutaneous telangiectasias [6]. Epidemiological studies on the AT group have provided evidence that patients carrying heterozygous mutations have a significantly increased risk of cancer [7]. The ATM, which is mutated in this disease, is a tumor suppressor gene located on chromosome 11q22 and encodes a 370 kDa serine/threonine protein kinase [8]. ATM, a member of the phosphodiethylinositol 3-kinase (PI3K)-related kinase (PIKK) family group, consists of the Tel1/ATM N-terminal motif (TAN), focal adhesion targeting (FAT), and PI3/PI4-kinase domains [9]. The ATM gene helps preserve the cell's genetic information by repairing broken strands in DNA [10]. During dormancy, ATM forms an inactive dimer structure in the nucleus and undergoes autophosphorylation to respond to DNA double-strand breaks. It is then transferred to chromatin to dissociate into active monomers [11]. Following activation, ATM functions by phosphorylating downstream effector proteins such as p53, MDM2, CHK2, H2AX, and BRCA1 to orchestrate cell death, the cell cycle, and transcription [12]. ATM is also involved in controlling many biological processes, including DNA repair, cell cycle checkpoint regulation, and programmed cell death, by activating the DNA damage reaction following the induction of DNA double-strand breaks. However, increasing evidence suggests that ATM-mediated phosphorylation is important in the response to many different types of stress [13]. *In vitro* studies have shown that oxidative stress can directly activate ATMs. ATM-dependent cell migration has been detected in different types of cancer, and in addition, ATM facilitates the release of interleukin-8 to enhance breast and lung cancer cell migration in response to oxidative stress [14]. ATM, phosphorylated by direct activation, is a kinase involved in cellular redox regulation of pentose phosphate (PP) and helps increase flux through the pentose phosphate pathway (PPP) [15]. Although ATM is known to have an important function in cancer cells, its role in signaling pathways remains unclear, making it a potential target. Therefore, researchers have investigated small-molecule ATM inhibitors that mimic the absence of ATM to identify cancer treatments.

The first selective ATM kinase inhibitor, KU-55933, is known as an ATM inhibitor frequently used in various cancer types. However, its use in *in vivo* studies has been limited due to its high lipophilicity [16]. On the other hand, the antitumor effects of various ATM inhibitors have been investigated in both *in vitro* and *in vivo* models. Again, a potent and selective ATM inhibitor, AZD-0156, which was previously in the clinical development phase, was developed [17]. However, as a result of the studies, AZD-1390, which is known as an important agent for carriers and has a stronger effect, was discovered due to the limited effect of AZD-0156. AZD-1390 is an improved version of AZD-0156 with an IC_{50} value of 0.00078 µmol/L in brain cancer cells for ATM inhibition [18]. AZD-1390 is a highly potent and selective ATM inhibitor currently in phase I clinical development in combination with radiation therapy (RT) for the treatment of glioblastoma (GBM) and brain metastases (NCT03423628) [18]. In the study by Durant et al., the AZD-1390 inhibitor was used to provide selective ATM inhibition in lung and glioma cancer cells. After 4 h of treatment with AZD-1390, a decrease in ATM phosphorylation was observed, while on the other hand, it was determined that the cells were directed to programmed cell death [19]. Our research provides a molecular approach to uncover the link between ATM and ovarian cancer. In this study, we investigated the impact of AZD-1390 on cell proliferation, colony formation, migration, ROS and cell death in ovarian cancer cell lines.

2. MATERIAL AND METHOD

2.1. Cell Culture and Environmental Conditions

Ovarian cancer cell lines SKOV-3 and OVCAR-3 were provided by the Bingöl University Cancer Research Group (BUKAG). SKOV-3 cells were cultured in 10% fetal bovine serum (FBS), while OVCAR-3 cells were cultured in RPMI 1640 medium containing 10% FBS supplemented with 64 µg/mL penicillin and 100 µg/mL streptomycin. All cells were incubated at 37°C in a humidified environment with 5% CO_2 for *in vitro* cell culture steps.

2.2. Cell Viability Test

The viability of AZD-1390-treated ovarian cancer cells was analyzed by WST-1 (4-[4-3-(4-Iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzenesulfonate) assay. Cells were seeded in 96-well plates ($3x10^3$ cells per well) and treated with various concentrations of AZD-1390 for 24 hours. Then, WST-1 test dye was added and after 2-3 hours of incubation, absorbance value was measured at 450 nm (Bio-Rad Benchmark, USA) [20].

2.3. Colony Formation Test

For the colony formation test, $3x10^3$ cells were seeded in 6-well plates. The next day, the cells were treated with AZD-1390 doses determined according to IC_{50} values. The plate containing the cells was incubated for 12 days in a humidified 37°C cell culture incubator containing 5% CO_2, and colony formation was observed under a microscope. After twelve days, the cells were washed with PBS. The plate was treated with a methanol-acetic acid (3:1) solution for 5 minutes. Then, they were exposed to 0.5% crystal violet dye for 10 min. Finally, colonies containing at least fifty cells were counted and statistically analyzed [21].

2.4. Wound Healing Test

After the confluency of ovarian cancer cells reached 90%, they were cultured in 12-well plates. After 24 hours of incubation, a straight line was drawn in the middle of the wells with a 200 µl pipette tip. The wells were gently washed with PBS to remove dead and motile cells, and treatment doses of AZD-1390 were added. The drawn areas were photographed with an inverted microscope at 0-24-48 hour intervals. The Image J version 1.50i program was used for measurements and to determine the migratory ability of cancer cells [22].

2.5. Measurement of Intracellular ROS

Ovarian cancer cell lines (2×10^5 per well) were seeded in 6-well plates. After 24 hours of treatment, cells were collected using a scraper and incubated in serum-free medium containing 10 mM DCFDA (Sigma-Aldrich) for 30 minutes at 37°C in the dark. PBS solution was added to each dose, and measurements were performed on a fluorescence spectrophotometer at a wavelength of 485–535 nm [23].

2.6. Acridine Orange/Ethidium Bromide (AO/EB) Staining

Ovarian cancer cells SKOV-3 and OVCAR-3 were incubated with AZD-1390 in a 5% CO_2 incubator at 37°C for 24 hours. Following the incubation period, the cells were treated with AO/EB (1:1) solution in the dark for 15 minutes. At the end of the period, the morphology of living and dead cells was observed under a fluorescence microscope [24].

2.7. Statistical Analysis

Statistical analysis was performed using the "One-Way ANOVA" method using multiple comparative Post Hoc Tests according to Tukey using the GraphPad Prism 10.4.1 program. $P<0.05$ was considered significant in the analyses.

3. RESULTS

3.1. AZD-1390 Decreases Cell Viability and Colony Formation in Ovarian Cancer Cell Lines

In this study, the antiproliferative effect of AZD-1390 on ovarian cancer cells (SKOV-3 and OVCAR-3) was carried out by cell viability and colony formation methods. WST-1 assay was used for cell viability assay. In line with the experimental conditions, AZD-1390 reduced the cell viability of ovarian cancer cell lines SKOV-3 and OVCAR-3 in a dose- and time-dependent manner (Figure 1A,B). Cell viability of SKOV-3 and OVCAR-3 treated with AZD-1390 for 48 hours decreased in a dose- and time-dependent manner (Figure 1C,D). It was shown that SKOV-3 (IC_{50} values for 24 h: 31.8225, and 48 h: 5.6344 µM) and OVCAR-3 (IC_{50} values for 24 h: 44.6181, and 48 h: 15.9741 µM) cells were sensitive to the AZD-1390 inhibitor. Given the activity of AZD-1390 in ovarian cancer cells, a 24-hour treatment period was determined to be sufficient, and therefore, this treatment period would be used in subsequent experiments. Subsequently, SKOV-3 and OVCAR-3 cell lines were incubated with the AZD-1390 inhibitor for 48 hours. Cell proliferation was then assessed using a colony formation assay. As shown in Figure 1E, a dose-dependent decrease in cell proliferation was observed.

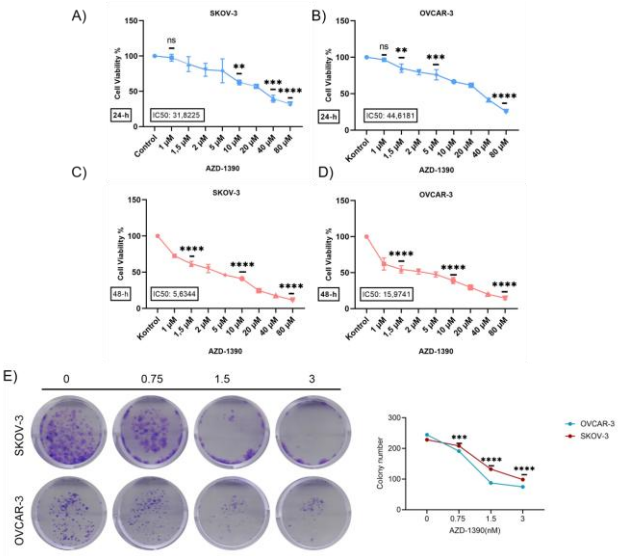

Figure 1. AZD-1390 inhibited the viability and reduced the proliferation of ovarian cancer cell lines. A,B) Cell viability of ovarian cancer cells (SKOV-3/OVCAR-3) was determined by WST-1 assay after 24 hours of treatment with AZD-1390 inhibitor. (n=3 replicates) C, D) Cell viability graphs of ovarian cancer cells after 48 hours of treatment with AZD-1390 inhibitor are shown. E) Colony formation images and proliferation analysis determined by colony formation assay of SKOV-3 and OVCAR-3 cell lines treated with AZD-1390 for 24 hours. Three replicates were performed in each group. Results were obtained using the One-Way ANOVA test. Statistical analyses were performed using the "One-Way ANOVA" method with multiple comparisons using the Post-Hoc Test according to Tukey using the GraphPad Prism 10.4.1 program. (*<0.05, **<0.01, ***<0.001, ****<0.0001, ns=not significant)

3.2. AZD-1390 Inhibits Cell Migration in Ovarian Cancer *In Vitro*

To determine whether AZD-1390 affected the ability of OVCAR-3 and SKOV-3 cells to migrate, we analyzed the images. We treated ovarian cancer cell lines with AZD-1390 (0-5-15-30 µM) and the components were used. Then, images were taken under an inverted microscope at 0-24-48 hour intervals. (Figure 2A,C) Figure 4B,D shows the statistical analyses of OVCAR-3 and SKOV-3 cells treated with AZD-1390, determined by the One-Way ANOVA test. While AZD-1390 treatment suppressed cell migration in the OVCAR-3 cell line at 48 hours, it was observed that it significantly suppressed the migration ability in SKOV-3 cells at 24 hours. (*<0.05, **<0.01, ***<0.001, ****<0.0001, ns=not significant)

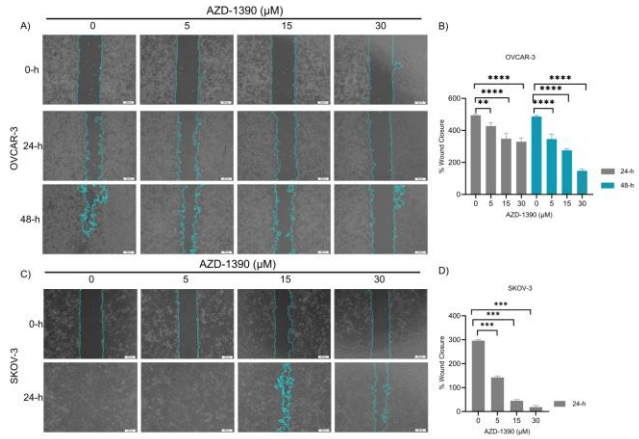

Figure 2. AZD-1390 inhibited the migration ability of cells. A) Wound healing test, images of the OVCAR-3 cell line were taken under a microscope after 0-24-48 hours of treatment with different doses of AZD-139. (original magnification 4x). A scratch was made in the middle of the cells in the petri and images were obtained under a microscope to determine whether the scratch would close in 48 hours to determine the migration ability of the cells. B) Wound closure analyses of OVCAR-3 were measured after treatment with AZD-1390 and microscope images taken at 24 (Gray bars) and 48 (Blue bars) hours were used. C) After treatment of the SKOV-3 cell line with AZD-1390, it was observed that the scratch closed in 24 hours (Gray bars) to determine the migration ability of the cells. Therefore, a 48-hour treatment was not applied. D) Statistical analysis of SKOV-3 cells obtained for 24 hours is shown. (*<0.05, **<0.01, ***<0.001, ****<0.0001, ns=not significant) Statistical analyses were performed using the "One-Way ANOVA" method with multiple comparisons using the Post-Hoc Test according to Tukey using the GraphPad Prism 10.4.1 program.

3.3. AZD-1390 Increases ROS Levels in SKOV-3 and OVCAR-3 Cells

Here, we evaluated the effect of AZD-1390 on ROS levels in OVCAR-3 and SKOV-3 cells (Figure 3A,B). Measurements were performed using a fluorescence spectrophotometer using DCFDA green fluorescent staining. The results were statistically calculated using the Graphpad program. AZD-1390 promoted ROS production in ovarian cancer cell lines. Our results statistically showed that AZD-1390 significantly increased the amount of ROS.

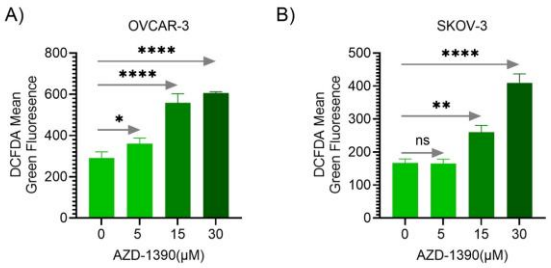

Figure 3. AZD-1390 increased ROS in ovarian cancer cells. A) OVCAR-3 and B) SKOV-3 cells were treated with DCFDA solution after 24 hours of AZD-1390 treatment. Then, ROS level was analyzed using fluorescence spectrophotometer. Statistical analysis of ROS levels in each group was performed. (*<0.05, **<0.01, ***<0.001, ****<0.0001, ns=not significant) Statistical analyses were performed using the "One-Way ANOVA" method with multiple comparisons using the Post-Hoc Test according to Tukey using the GraphPad Prism 10.4.1 program.

3.4. AZD-1390 Promotes Apoptotic Cell Death in Ovarian Cancer Cells

The AO/EB staining assay was used to determine whether the growth inhibition of AZD-1390 in ovarian cancer cells was associated with cell death. Figure 4A shows microscopic images of OVCAR-3 and SKOV-3 cell lines after treatment with AZD-1390 (0-5-15-30 µM). Figure 4B,C shows statistically determined photographs obtained from the microscope images. Microscope images and statistical analysis of cells treated with AZD-1390 for 24 hours showed that color changes increased dose-dependently and induced apoptotic cell death of cells in both cell lines (Figure 4).

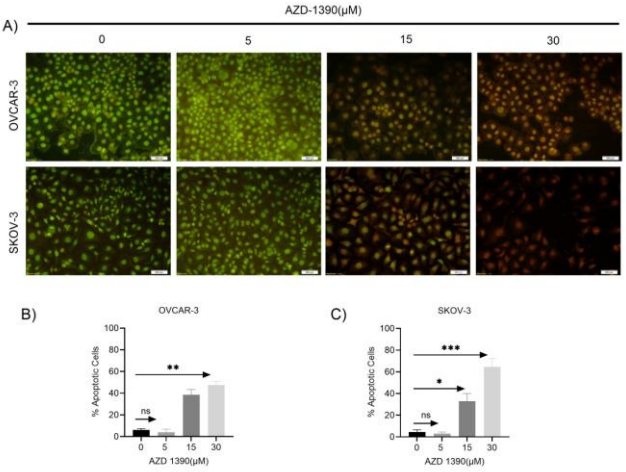

Figure 4. AZD-1390 promoted apoptotic death of ovarian cancer cell lines. A) SKOV-3 and OVCAR-3 cells were treated with AO/EB solution 24 hours after AZD-1390 treatment. They were then visualized under a fluorescence microscope (Original magnification 20x). Green fluorescence in AO/EB solution indicates live cells, while orange-red fluorescence indicates dead cells. B,C) Percentage of apoptotic cell intensities in SKOV-3 and OVCAR-3 cell lines showed that cell death occurred in SKOV-3 and OVCAR-3 cells after 24 hours of treatment with AZD-1390, especially at a dose of 30 µM. Statistical analyses were performed using the "One-Way ANOVA" method with multiple comparisons using the Post-Hoc Test according to Tukey using the GraphPad Prism 10.4.1 program. (*<0.05, **<0.01, ***<0.001, ****<0.0001, ns=not significant)

4. DISCUSSION AND CONCLUSION

Ovarian cancer poses a significant diagnostic and therapeutic challenge among modern gynecologic cancers. Recent studies have identified the mutant ATM gene as a significant risk factor, particularly in ovarian and breast cancers. ATM inhibition has been found to impair ATM-mediated DNA repair, leading to HRR deficiency in ovarian cancer cells. ATM is a gene encoding a 370 kDa serine/threonine protein kinase located on chromosome 11q22. ATM activation acts by phosphorylating downstream effector proteins such as p53, MDM2, CHK2, H2AX, and BRCA1 to regulate cell death, the cell cycle, and transcription. ATM is known to have an important function in cancer cells, but its role in signaling pathways remains unclear, making it a potential target. New treatment strategies are needed to overcome this situation [32]. Researchers believe that targeting ATM may be considered a suitable strategy for synthetic cancer cell killing treatments. In recent years, many ATM inhibitors have been discovered and have been used in clinical trials. The first specific ATM kinase inhibitor, KU-55933, was used in combination with Olaparib in endometrial cell lines in the study of Zhang et al. As a result of the experiments, it was shown that KU-55933 not only prevented colony formation and cell migration but also supported apoptosis induced by Olaparib [11]. Pharmacy company in collaboration with well-known laboratories worldwide, developed a potent and selective ATM inhibitor, AZD-0156. However, due to the limited efficacy of AZD-0156, numerous studies have identified an orally bioavailable ATM inhibitor, AZD-1390, developed by AstraZeneca [19]. AZD-1390 is a leading PI3K inhibitor due to its high selectivity, oral bioavailability, and being the leading clinical ATM inhibitor. The first phase 1 study of AZD-1390 (NCT03215381) was successfully completed in 2018. An early phase 1 study was also conducted by Gulliver et al. in 2022 [33].

The effects of AZD-1390 on cell viability and cell proliferation were evaluated using cell culture assays on ovarian cancer cell lines. The results showed that AZD-1390 (<30 μM) effectively reduced the viability of ovarian cancer cell lines OVCAR-3 and SKOV-3. Since there was an effective decrease especially in the 24-h cell line, 24-h treatment period was used in other experiments. On the other hand, a clonogenic assay was performed to determine the effect of AZD-1390 on cell proliferation after 24 hours of treatment in ovarian cancer cells. The results showed that AZD-1390 inhibited the proliferation of OVCAR-3 and SKOV-3 cell lines in a dose-dependent manner. Chen et al. also determined clonogenic survival following treatment with AZD-1390 in glioblastoma cells. The results obtained determined that AZD-1390 induced by radiotherapy reduced survival in GBM cell lines [34]. In a study different from ours, Nadkarni et al. investigated the effect of ATM inhibitor KU-55933 on Temazolamide (TMZ) sensitivity in GBM cells. It was observed that KU-55933 selectively sensitized the cells in U251 and U87 cell lines, but it was shown that it did not sensitize GBM cells resistant to TMZ [35]. Several studies have shown that ATM expression is associated with epithelial-mesenchymal transition (EMT) and metastatic potential of cancer cells [20]. Therefore, we examined the efficacy of AZD-1390 on the migration ability of ovarian cancer cell lines using a wound healing assay. We found that AZD-1390 treatment effectively slowed down wound closure. The obtained data showed that AZD-1390 treatment in ovarian cancer cells inhibited cell migration. Wang et al. who had similar results to our study, treated SKOV-3 cells with the ATM inhibitor KU-60019 for 24 h. The obtained results showed that it significantly inhibited cell migration [36].

ATM kinase is activated in response to excessive ROS production and phosphorylates PEX5, which promotes ubiquitination. On the other hand, the ROS signaling cascade activates the DNA damage response pathway, particularly via the ATM axis [37,38]. Considering the effect of ATM on ROS activation, we examined the effect of AZD-1390 on ROS using DCFDA dye to determine the effect of ATM inhibition on the amount of ROS. As a result of the study, we clearly showed that AZD-1390 effectively increased the amount of ROS in a dose-dependent manner compared to the untreated group in OVCAR-3 and SKOV-3 cell lines. ATM has emerged as a major stress-responsive protein that is directly and independently activated by ROS. As a result, mitochondrial apoptosis is initiated through a series of downstream pathways [39]. In addition, as shown in the study by Deniz et al. AZD-1390 alone increased apoptosis in breast cancer cells [35]. The AO/EB staining results in our study also statistically determined that AZD-1390 leads to cell death in a dose-dependent manner. These results show that AZD-1390 treatment causes a significant increase in programmed cell death apoptosis in OVCAR-3 and SKOV-3 cell lines, in line with previous articles.

Overall, the results in this study demonstrated that AZD-1390 inhibits cell survival, proliferation, and migration. Ovarian cancer cell lines treated with AZD-1390 exhibit antitumor activity by increasing SKOV-3 and OVCAR-3 ROS levels and inducing apoptotic cell death. While AZD-1390 treatment has shown promising results in ovarian cancer cell lines, further studies are needed to determine the underlying mechanisms.

In general, the data obtained as a result of this study show that ATM inhibitor AZD-1390 reduces cell viability and proliferation, inhibits the migration ability of cells and directs them to programmed cell death apoptosis. Although promising results were obtained in ovarian cancer cell lines OVCAR-3 and SKOV-3 treated with AZD-1390, further studies are needed to address the underlying molecular mechanisms and to strengthen our hypothesis. In future studies, the expression levels of proteins in certain pathways and gene expression levels should be examined. On the other hand, studies should be conducted with animal models using different drug combinations. In line with these approaches, more reliable results with potential clinical implications can be obtained.

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