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HS-173, a novel PI3K inhibitor enhances radiosensitivity of breast cancer cells

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► ***Original article***

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ABSTRACT

Background: The development of radiosensitizers that modulate activated signaling pathways has enhanced effective cancer treatment via radiation therapy. The phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT) pathway induces cancer progression and radioresistance. Therefore, we investigated if HS-173, a novel PI3K inhibitor, could increase the radiosensitivity in breast cancer cells. ***Materials and Methods***: Breast cancer cell lines (MCF-7, BT-474, and T47D, MDA-MB-231) were exposed to radiation (2–8 Gy). After irradiation, cell viability was assessed using the MTT assay. MDA-MB-231 cells were exposed to radiation (5 Gy) alone and/or in combination with HS-173 (1 μM). After treatment, the levels of PI3K/AKT signaling protein were measured using western blotting. The radiosensitivity of HS-173 was assessed using a clonogenic assay and flow cytometry. ***Results***: We observed that HS-173 decreased the radiation-induced phosphorylation of AKT in MDA-MB-231 cells and increased their radiosensitivity in the clonogenic assay. Upon investigation of the mechanism underlying the enhanced radiosensitivity by HS-173, we observed a significant increase in the IR-induced G2/M cell cycle arrest and apoptosis pathway components, including poly (ADP-ribose) polymerase (PARP-1) and cleaved caspase-3. It can be concluded that HS-173 significantly improved radiosensitivity by inducing apoptosis and G2/M arrest in radio-resistant breast cancer cells. ***Conclusion***: HS-173 may be applied as a radiosensitizer with promising potential in radio-resistant breast cancer treatment.

INTRODUCTION

Breast cancer, the most common malignancy in women, is currently the second leading cause of cancer-related death in women [1] Breast cancer cells have three important receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). In most cases, breast cancers which are treated depending on their receptor type show a better prognosis [2]. Although significant progress has been made in breast cancer treatment, only a few targeted therapies are available for patients with estrogen receptor (ER)-negative and triple-negative breast cancer (TNBC), with conventional surgery, radiation therapy, and chemotherapy being the primary treatment options [3]. In particular, TNBC does not have any breast cancer-related receptor, resulting in metastasis and higher instances of death. Additionally, it is commonly resistant to the typical anti-cancer agents used [4]. With no targeted treatments available currently, conventional cytotoxic chemotherapy followed by adjuvant radiation therapy is the standard of care for patients with TNBC. Therefore, there is an urgent need to develop treatment strategies to improve these limited therapeutic options.

For breast cancer, one of the therapeutic options is radiotherapy, in addition to surgery and chemotherapy. It is a critical component in multimodal management of breast cancer patients [5]. Breast cancer patients who received radiation therapy achieved a complete cure with a significantly increased survivability period [6]. However, a substantial fraction of patients acquired radioresistance, which significantly inhibited the effectiveness of this therapy. In the cases with TNBC, the patients who received standard adjuvant chemotherapy plus the radiation therapy had a decreased risk of locoregional recurrence compared to those treated with chemotherapy alone. However, many breast cancer patients fail to undergo radiotherapy and chemotherapy for the tumor [7-10]. Thus, improvement in radiosensitivity plays an important role in breast cancer therapy. The development of novel radiosensitizing agents could provide substantial benefits for increasing the efficiency of radiosensitivity.

To increase radiosensitivity by overcoming radioresistance, many potential molecular targets

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have been validated to date [11]. The phosphoinositide 3-kinase (PI3K) pathway is important for cell growth, proliferation, and survival, and has matured as a clinical therapeutic target for breast cancer [12]. In addition, the PI3K/AKT pathway is known to activate resistance to radiotherapy [13, 14]. Inhibition of the PI3K/AKT pathway has been linked to radiosensitivity in various cancers including non-small cell lung cancer, glioblastoma, head and neck squamous cell carcinoma, and colorectal cancer [15-18]. In this regard, PI3K inhibitors exert synergistic effects in combination with radiation, resulting in improved radiosensitization [19, 20].

This study aims to screen radiation-resistant breast cancer cell lines and investigate if HS-173, a novel PI3K inhibitor, enhances radiosensitization by inhibiting the PI3K/AKT pathway.

MATERIALS AND METHODS

Cell lines & materials

MCF-7, BT-474, T47D, and MDA-MB-231 cells were obtained from the Korean Cell Line Bank (KCLB, Seoul, South Korea) and cultured in an RPMI media supplemented with 10% FBS and 1% penicillin/streptomycin. The cell culture media, FBS, penicillin/streptomycin, and all the other agents used in the cell culture studies were purchased from GIBCO (Grand Island, NY, USA). The cells were incubated in a CO_2 incubator at 37°C in a controlled humidified atmosphere composed of 95% air and 5% CO_2. The imidazopyridine derivative, ethyl 6-(5-(phenylsulfonamido) pyridin-3-yl) imidazo [1,2-a] pyridine-3-carboxylate (HS-173), a new PI3Ka inhibitor, was synthesized as described in our previous studies [21-26]. For all *in-vitro* studies, HS-173 was dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM before use.

Irradiation

The cells were treated with g-rays from ^{137}Cs irradiation source (Model 68; JL Shepherd & Associates, Glenwood, CA, USA). The ^{137}Cs irradiation source emitted 3-4 Gy/min.

Cell viability and Clonogenic assay

Breast cancer cells were treated with HS-173, with or without radiation. To investigate if the inhibition of PI3K/AKT pathway by HS-173 is radiosensitive, we assessed the survival fraction in MDA-MB-231 cells upon treatment with HS-173 (1 μM or 10 μM) and radiation. MDA-MB-231 cells were pre-treated with HS-173 for 2 h followed by irradiation. After 14 days, we performed a clonogenic assay to determine the cell survival. The colonies were observed and then fixed in PFA (4%) and crystal violet (0.5%). After counting the colonies, the data were processed to calculate the plating efficiencies compared with non-irradiated cells.

Western blotting

The PI3K/AKT signaling pathway is upregulated by irradiation in many types of cancer, which is correlated with resistance to radiotherapy [22, 27]. To confirm whether irradiation induces the PI3K/AKT signaling pathway in breast cancer cells, we assessed the activation of the PI3K/AKT signaling pathway after irradiation in a time-dependent manner.

The protein was prepared from the breast cancer cells using the RIPA buffer adding the protease inhibitor and phosphatase inhibitor (GenDEPOT, Barker, TX, USA) for 10 min. Total protein in the whole cells was quantified using a BCA solution (Sigma-Aldrich, Ohio). Briefly, 30 μg of protein was loaded on 8% and 15% Bis-Tris polyacrylamide gels, at 100 V using SDS-PAGE. It was then transferred to the nitrocellulose membranes. After blocking with 5% skim milk, the membranes were incubated with the primary antibodies for 24 h: p-AKT, AKT, p-mTOR, mTOR, PARP-1, cleaved caspase-3, Bcl-2, and a-tubulin (Cell Signaling Technology, MA, USA). After incubation with primary antibodies, the membranes were washed three times and then attached with horseradish peroxidase (HRP)-conjugated secondary antibodies (Santa Cruz Biotechnology, Dallas, TX, USA) for 1 h. Antibody binding was detected using enhanced chemiluminescence (ECL) reagents (Bio-Rad, Hercules, CA, USA).

TUNEL assay

A TUNEL assay was performed using an APO-BrdU™ TUNEL assay kit as per the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA). Briefly, paraformaldehyde (1%) was added to single-cell suspension of MDA-MB-231 cells for 1 h at 4°C. Apoptotic cells were labeled using the APO-BrdU TUNEL assay kit and then analyzed using FACS cytometry (BD Biosciences, San Jose, CA, USA). The data were analyzed using FlowJo software (Tree Star, Inc., San Carlos, CA, USA).

Flow cytometry

To investigate the mechanism through which the HS-173 induced radiosensitization in MDA-MB-231 cells, we analyzed the cell cycle distribution after the combined treatment. Based on our previous study [22], we hypothesized that HS-173 would lead to the accumulation of the G2/M phase in irradiated-MDA-MB-231 cells. For fixation of cells, cold ethanol (70%) was added to a single- cell suspension of MDA-MB-231 cells at -25°C for 24 h. After incubation for 24 h, the cells were treated with a mixture of propidium iodide (PI, 50 mg/mL) and RNase A (100 mg/mL) at 37°C for 30 min in the dark. Cells were labeled using PI solution and then analyzed using a FACS cytometer (BD Biosciences, San Jose, CA, USA). The data were analyzed using FlowJo software (Tree Star. Ashland, OR, USA).

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Statistical analysis

Statistical calculations were performed using the SPSS software for Windows (version 10.0; SPSS, Chicago, IL, USA). Data are presented as mean (±SD) and were subjected to either unpaired Student's *t*-test or analysis of variance (ANOVA). Statistical significance was set at *P*-value ≤ 0.05. The results were compared using the Student's *t*-test.

RESULTS

Radio-resistant breast cancer cell lines

To determine if the breast cancer cell lines acquired resistance to radiation, several breast cancer cells including the MCF-7, BT-474, T47D, and MDA-MB-231 were irradiated with 2-8 Gy for 72 h. Irradiation-induced cell death was observed at 8 Gy in these cells. However, in the case of TNBC MDA-MB-231 cells, irradiation with 8 Gy failed to induce cell death compared to other breast cancer cell lines (figure 1), indicating that MDA-MB-231 cells are resistant to irradiation. These results imply that radiation-resistant breast cancer cells require radiosensitizing agents to overcome this resistance.

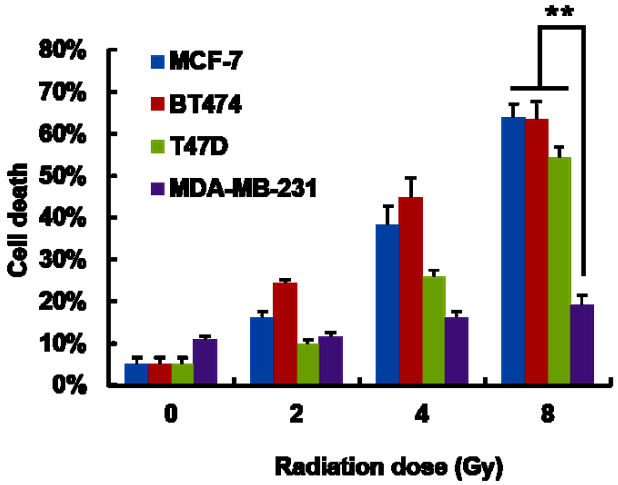


Figure 1. Selection of radio-resistant breast cancer cell lines. Human breast cancer cells MCF-7, BT-474, T47D, and MDA-MB-231, were irradiated with the indicated doses (0-8 Gy). Cell death was measured using the MTT assay. Data are expressed as means (±SD) from three independent experiments (**P<0.01).

Activation of AKT/mTOR pathway through irradiation in radio-resistant breast cancer cells

Irradiation significantly increased the expression of p-AKT and p-mTOR, indicating that irradiation activates the critical components of the PI3K/AKT signaling pathway in human MDA-MB-231 radio-resistant breast cancer cells (figure 2A). Our previous studies showed that HS-173 inhibited the PI3K/AKT signaling pathway in various cancer cell types [22, 24-26, 28]. Accordingly, we investigated if HS-173 inhibited radiation-induced activation of the PI3K/AKT signaling pathway in MDA-MB-231 cells. It was found that HS-173 effectively inhibited the radiation-induced phosphorylation of AKT in these cells (figure 2B). These results suggest that HS-173 enhances radiosensitivity in radioresistant breast cancer cells.

Radiosensitization of HS-173 in MDA-MB-231 cells

The survival fraction of MDA-MB-231 cells was slightly reduced by irradiation in a dose-dependent manner (figure 3). Conversely, HS-173 significantly enhanced the radiosensitivity of MDA-MB-231 cells under irradiation, indicating that inhibition of the PI3K/AKT pathway by HS-173 may be related to an increase in radiosensitivity (figure 3).

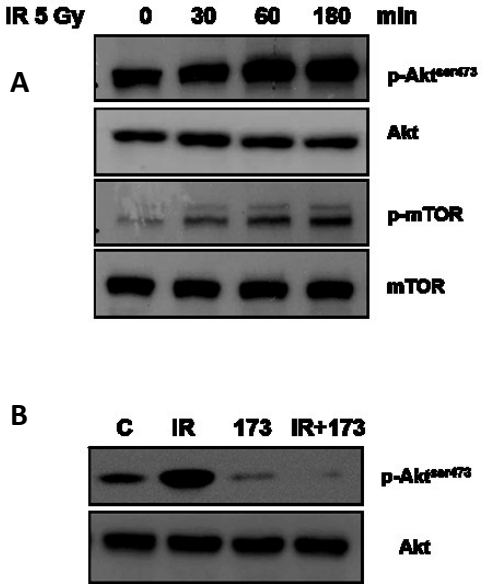


Figure 2. Radiation induced the PI3K pathway in breast cancer cells. **A.** MDA-MB-231 cells were irradiated with 5 Gy for the indicated duration (0–180 min). Under radiation conditions, high levels of expression of p-AKT and p-mTOR were observed in MDA-MB-231, as seen in the results of western blotting. **B.** MDA-MB-231 cells were exposed to radiation (5 Gy) and/or HS-173 (1 μM). After 3 h, p□AKT levels were assessed using western blotting.

Induction of G2/M arrest by HS-173 in irradiated MDA-MB-231 cells

When we analyzed the cell cycle distribution after the combined treatment, it was observed that the radiation increased the G2/M phase of the population for 24 h in MDA-MB-231 cells. However, when HS-173 was combined with radiation, a higher degree of G2/M arrest (56%) was observed compared to that with radiation-treatment alone (42%, figure 4).

Induction of apoptotic cell death through HS-173 and radiation combination treatment

Our previous studies showed that HS-173 induces apoptotic cell death in various cancer cell types [25, 28]. As the combined treatment with HS-173 and radiation significantly reduces the cell proliferation, we investigated the apoptotic effects of this combination in MDA-MB-231 cells. MDA-MB-231

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cells were pretreated with HS-173 and then irradiated. Notably, combination treatment with HS-173 and radiation resulted in an increase in apoptotic cell death compared to that in the radiation only treatment (figure 5A). These results were confirmed by assessing the apoptosis-related proteins, which revealed that the combined treatment with HS-173 and radiation increased the levels of cleaved caspase-3 and cleaved PARP. However, it decreased the expression levels of anti-apoptotic Bcl-2 compared to their levels in the radiation only treatment. These results demonstrate that HS-173-induced radiosensitivity enhanced the apoptosis in MDA-MB-231 cells (figure 5B).

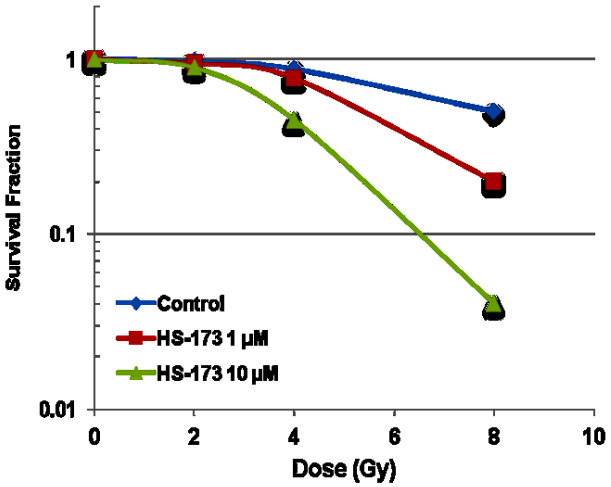


Figure 3. Clonogenic survival assay with radiosensitization by HS-173 in MDA-MB-231 cells. (A) MDA-MB-231 were treated with various concentrations of HS-173 (1 μM or 10 μM) for 2 h and then irradiated with the indicated doses (0–8 Gy). After 2 h, the media were changed, and the cells were processed for clonogenic survival assays at the end of the experiments (14 days). Colonies were counted using a cut-off value of 50 viable cells per colony.

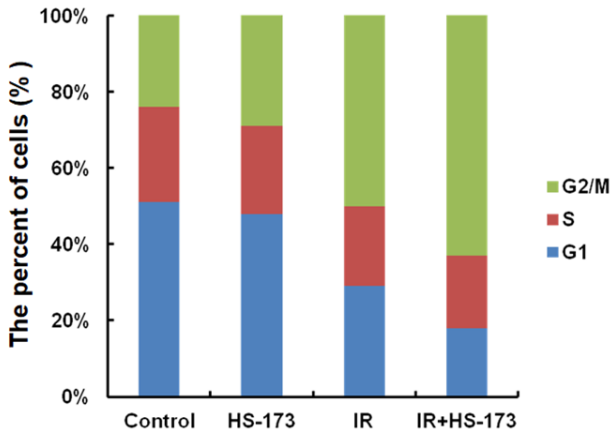


Figure 4. HS-173 triggered IR-induced cell cycle arrest at G2/M phase. MDA-MB-231 cells were treated with HS-173 (1 μM), irradiated with 5 Gy for 24 h, stained with PI, and analyzed through flow cytometry. Quantitative PI staining data is presented as a percentage of cell cycle distribution.

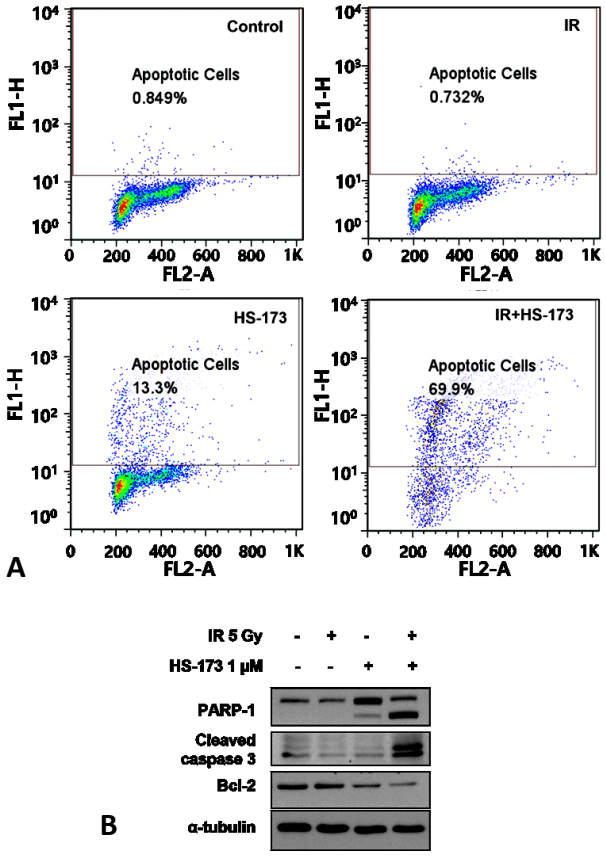


Figure 5. HS-173 sensitized MDA-MB-231 cells to irradiation. **A.** MDA-MB-231 cells were treated with HS-173 (1 μM) and irradiated with 5 Gy for 24 h. DNA fragmentation in MDA-MB-231 cells was evaluated through flow cytometry and TUNEL staining. **B.** Western blot analysis for apoptosis-related protein (PARP, cleaved caspase-3, and Bcl-2).

DISCUSSION

Breast cancer continues to be a major cancer in women [29]. Surgical removal of the tumor mass considerably reduces the quality of life [30]. Chemotherapy and radiotherapy are used to intensify the therapeutic effects. Although radiotherapy is the common treatment of choice for breast cancer, acquired radiation resistance is considered a major obstacle as it limits effective treatment [31]. The aim of this study was to evaluate the radiosensitizing effect of HS-173 and to investigate the underlying functioning mechanisms of agent functions. This study revealed that HS-173 is capable of inhibiting the proliferation of radiation-resistant triple-negative breast cancer MDA-MB-231 cells and induces G2/M arrest, in addition to apoptosis by inhibiting the PI3K/AKT pathway, particularly in combination with radiation treatment.

The PI3K/AKT pathway is associated with radiation resistance mechanisms such as a decrease in intrinsic radiosensitivity and cancer cell proliferation. In signaling pathways, PI3K/AKT

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signaling is a key modulator in cancer cell growth and proliferation [32]. Additionally, several treatment modalities, including radiotherapy, can stimulate the survival pathway in breast cancer [33]. Regulation of this signal transduction pathway may have important implications in the management of breast cancer. Strong and independent relationships were observed between the activated AKT and treatment results in clinical trials [34, 35]. Direct targeting and inhibition of this pathway could increase radiosensitivity by inhibiting radiation-induced cellular defense mechanisms, particularly in cancers that have activated PI3K/AKT signaling. PI3K inhibitors have been shown to enhance the radiation sensitivity of human tumor cells [36, 37]. In addition, Guo *et al.* reported that LY294002, a PI3K inhibitor inhibited triple-negative breast cancer MDA-MB-231 cell proliferation by blocking the PI3K/AKT pathway. It shows that the inhibitor of the PI3K/AKT pathway plays an important role in blocking breast cancer development [38]. Until now, PI3K inhibitors have not achieved their expected therapeutic efficacy in clinical trials, however, several studies have demonstrated that combined treatment using the novel PI3K inhibitors is a promising combination strategy to maximize the therapeutic effect substantially [39]. Our previous studies have demonstrated that HS-173 inhibits cell proliferation/ cell growth in various cancer cells, including the pancreatic cancer cells, where it specifically enhances radiosensitization [22, 24, 28]. Accordingly, we expected that HS-173 could increase radiosensitivity in MDA-MB-231 breast cancer cells, which were identified as radiation-resistant cells amongst other breast cancer cell lines, such as MCF-7, BT-474, and T48D. HS-173 augmented the radiation effect in MDA -MB-231 cells by conferring radiation resistance and inhibiting PI3K/AKT signaling, which was significantly activated by radiation.

Many reports suggest that a combination of PI3K inhibitors and radiation leads to cell cycle arrest [27, 40, 41]. The G2/M phase plays a key role in DNA synthesis and repair. Therefore, G2/M arrest could enhance cell damage and increase radiosensitization. In our study, because the combination of HS-173 and radiation synergistically increased the therapeutic efficacy by blocking cell proliferation compared to that with radiation treatment alone, we hypothesized that HS-173 could enhance G2/M phase accumulation during the cell cycle. As expected, HS-173 showed a radiosensitization effect as an increase in the G2/M phase accumulation was observed. In addition, HS-173 enhanced the radiation-induced apoptosis, as evidenced by increased levels of PARP-1 and caspase-3, as well as TUNEL-positive cells, compared to that in the cells treated with HS-173 or radiation alone. The radiosensitizing effect of HS-173 may be mediated by numerous molecular pathways. The results of this study indicate that cell cycle arrest and apoptosis are the primary effects of HS-173 treatment.

CONCLUSION

This study demonstrates that HS-173 affects the proliferation of MDA-MB 231 cells through radiation resistance, which is associated with changes in cell cycle distribution. Additionally, HS-173 induces apoptosis in radio-resistant breast cancer cells, indicating that HS-173 could be a potential radiosensitizer for radio-resistant breast cancer in combination with radiotherapy.

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***Ethical consideration*:** The authors declare no conflict of interest.

***Author contributions*:** Experiments were performed by Lee H, Park JH, and Jung KH and were designed by Lim JH and Hong SS.

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