Breast Cancer: Targets and Therapy

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SHORT REPORT

Role of AURKB Inhibition in Reducing Proliferation and Enhancing Effects of Radiotherapy in Triple-Negative Breast Cancer

Sierra Pellizzari[1], Harjot Athwal[1], Anne Claudine Bonvissuto[1,2], Armen Parsyan[1–4]

[1]Department of Anatomy and Cell Biology, Western University, London, ON, Canada; [2]Verspeeten Family Cancer Centre, London Health Sciences Centre, London, ON, Canada; [3]Department of Oncology, Western University, London, ON, Canada; [4]Department of Surgery, St Joseph's Health Care and London Health Sciences Centre, Western University, London, ON, Canada

Correspondence: Armen Parsyan, Department of Surgery, St Joseph's Health Care London, Room D1-104, 268 Grosvenor Street, London, ON, N6A 4V2, Canada, Tel +1-519-646-4831, Email aparsyan@uwo.ca

Abstract: Breast cancer is a leading cause of cancer-related deaths in females. Triple-negative breast cancer (TNBC) subtype is the most aggressive form of breast cancer that lacks biomarkers and effective targeted therapies. Its high degree of heterogeneity as well as innate and acquired resistance to treatment creates further barriers in achieving positive clinical outcomes in TNBC. Thus, development of novel treatment approaches in TNBC is of high clinical significance. Multimodality approaches with targeted agents and radiotherapy (RT) are promising for increasing efficacy of treatment and circumventing resistance. Here we examined anticancer effects of the Aurora Kinase B (AURKB) inhibitor AZD1152 as a single agent and in combination with RT using various TNBC cell lines, MDA-MB-468, MDA-MB-231 and SUM-159. We observed that AZD1152 alone effectively inhibited colony formation in TNBC cell lines. The combination of AZD1152 at IC50 concentrations together with ionizing radiation further reduced colony formation as compared to the single agent treatment. Our data support the notion that inhibition of the AURKB pathway is a promising strategy for treatment and radiosensitization of TNBC and warrants further translational studies.

Plain Language Summary: Breast cancer is a leading cause of cancer death in women globally. The triple negative breast cancer subtype confers the poorest oncologic outcomes and requires novel treatment approaches. Development of new therapeutics as well as combination treatments with radiation are crucial. Aurora Kinase B (AURKB) protein regulates cell division that is often altered in breast cancer, contributing to tumor pathogenesis. This study examined the combination of an AURKB inhibitor, AZD1152, with radiation therapy, compared to single-agent treatments, in treating triple negative breast cancer cells. Our results show that AZD1152 and ionizing radiation alone were able to delay cancer cell proliferation effectively. However, their combination further significantly inhibited cell proliferation compared to single-agent treatments. This suggests that further studies on this combination would be valuable in developing novel treatment strategies for breast cancer.

Keywords: breast cancer, Aurora Kinase B, AZD1152, radiation, combination treatment, multimodality treatment, AURKB

Introduction

Breast cancer is the world's most prevalent cancer and a leading cause of cancer-related mortality in females, with 2.3 million women diagnosed and 685,000 deaths globally in 2020.[1] Some of its subtypes, such as triple negative breast cancer (TNBC), represent more aggressive phenotypes. Lack of common biomarkers and effective targeted therapies, as well as innate and/or acquired resistance to radiotherapy (RT) and chemotherapy[2–4] are important contributors to poor oncologic outcomes in TNBC. Developing new treatment strategies is therefore of critical importance. RT is a key modality for local disease control of breast cancer in the adjuvant and metastatic settings. It might also have advantages in the neoadjuvant setting to reduce tumour burden, facilitate surgical resection and induce chemosensitization of cancer.[5,6] Inherited or induced radioresistance is

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the major barrier to the effective control of disease and this may be overcome by the use of radiosensitizing agents.[7] Combination treatments with chemotherapeutic or targeted agents and RT to synergize effects of each individual treatment can potentially improve anti-tumour activity and oncologic outcomes.[7–10]

RT is known to induce genomic instability.[7,11] Compounds that target proteins controlling genomic stability might enhance effects of RT and help in overcoming radioresistance. One such protein, Aurora kinase B (AURKB), has been shown to be overexpressed in TNBC,[12] associated with increased familial breast cancer risks,[13] reported as a prognostic factor for TNBC[14] and associated with resistance to chemotherapy.[15] AURKB plays a role in metaphase and is an essential component of the chromosome passenger complex, chromosome segregation and cytokinesis; dysregulation of which causes abnormal cell division and aneuploidy, a hallmark of cancer.[16] Various compounds have been developed to target AURKB in cancer. One such highly selective AURKB inhibitor, AZD1152 (Barasertib), has been shown to be an effective antineoplastic agent in breast cancer[17–19] acting through induction of mitotic catastrophe, polyploidy and apoptosis.[17] Therefore, combination of RT with an AURKB inhibitor may further enhance genomic instability in TNBC and eventually cell death. AZD1152 has been shown to enhance radiosensitivity in other cancers, such as prostate[20] and colon cancers.[21,22] Recently, an abstract has been published, suggesting that Barasertib-HQPA induces radiosensitization in murine 4T1 TNBC cells.[23] However, to our knowledge, the anticancer effects of the combination of AURKB inhibition by AZD1152 or other agents with radiation in human breast cancer has never been studied. In this study, we aimed to test if the combination of RT with AZD1152 leads to enhanced anticancer effects in TNBC cell lines.

Materials and Methods

The MDA-MB-468 cell line was obtained from Dr. Ann Chambers (London Health Science Centre, London, Canada) and was cultured in α-MEM + 10% fetal bovine serum (FBS). The MDA-MB-231 cell line was obtained from Dr. Ann Chambers (London Health Science Centre) and was cultured in DMEM:F12 + 10% FBS. The SUM-159 cell line (Asterand Inc., Detroit, MI) was cultured in HAMS:F12 + 5% FBS, 0.5% insulin, 0.1% hydrocortisone and 1% HEPES. All cell lines were authenticated by the short tandem repeat (STR) profiling (using 9 markers). AZD1152 (Cat. No. S1147) was obtained from SelleckChem (Pennsylvania, USA). RT was performed using the Cobalt-60 radiation unit at the London Regional Cancer Program. Doses of RT and drug concentrations were selected by determining the ID50 or IC50 respectively for each cell line using dose response curves. Colony formation assays (CFA) were performed as previously described.[24] Briefly, cells were seeded in 6 well plates at colony forming density (52 cells/cm^2 for MDA-MB -231, SUM159, and 104 cells/cm^2 for MDA-MB-468). Adhered cells were treated with RT 16–20 hours later followed immediately by drug or vehicle control-supplemented media at the indicated doses, then grown for 7–14 days prior to fixation with acetone:methanol (1:1 vol/vol) and stained with 0.5% crystal violet in ddH_2O. Plates were imaged, colonies consisting of ≥50 cells were counted, and numbers were compared to vehicle control. Experiments were performed at least in triplicate. Synergy was assessed using SynergyFinder software (version 3.0)[25] using the Bliss score.

Statistical analysis was performed using GraphPad Prism Software (Dotmatics, San Diego, USA). IC50/ID50 doses of compounds and RT were calculated from single-agent dose response curves using a nonlinear regression model. Comparison of control, single agent and combination effects for CFA was performed using Two-Way ANOVA. Statistical significance was defined as $p \leq 0.05$.

Results

Effects of Combination Treatment with AZD1152 and Radiation in TNBC Cell Lines

We determined IC50 (for AZD1152) for each cell line using CFA (Figure 1). Based on our previous data, we used RT doses close to the therapeutically relevant dose of ID50 (2Gy of RT with MDA-MB-231 and MDA-MB-468 cells and 5Gy of RT with SUM-159 cells). Since different cell lines exhibited a different IC50 to AZD1152, we used a concentration of 15 nM for MDA-MB-231, 14nM for MDA-MB-468, and 124nM for SUM-159 cells. We then assessed efficacy of and differences in the combinatorial effect of AZD1152 and RT using these treatment parameters.

In MDA-MB-231 (Figure 2A), single agent treatment with AZD1152 resulted in a 46.9% (standard deviation, SD = 7.3%) decrease in colony formation (CF); 2 Gy of RT reduced CF by 17.5 ± 4.1%, while simultaneous combination

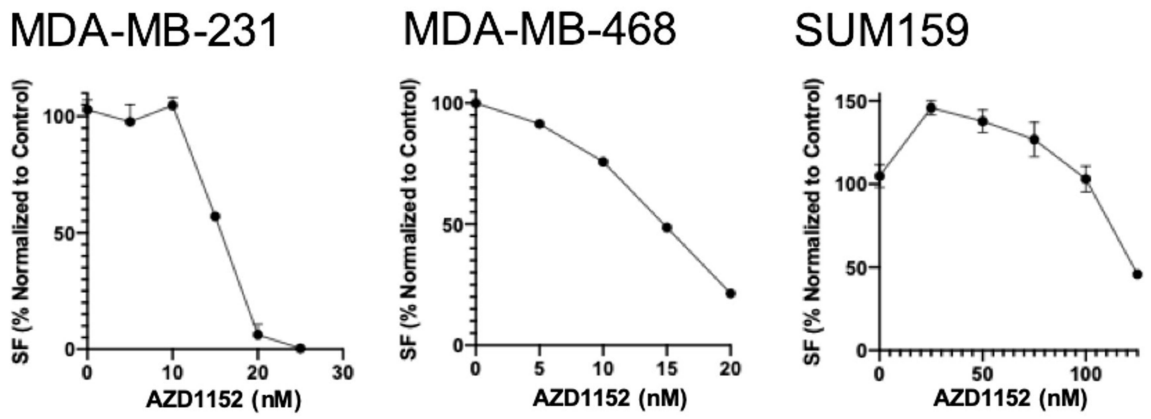

Figure 1 Effects of single agent AZD1152 at increasing concentrations on colony formation in TNBC cell lines. Dose response curves were generated for AZD1152 in studied cell lines. IC50 values were determined using a nonlinear regression model in GraphPad Prism software.
Abbreviation: SF, Surviving Fraction.

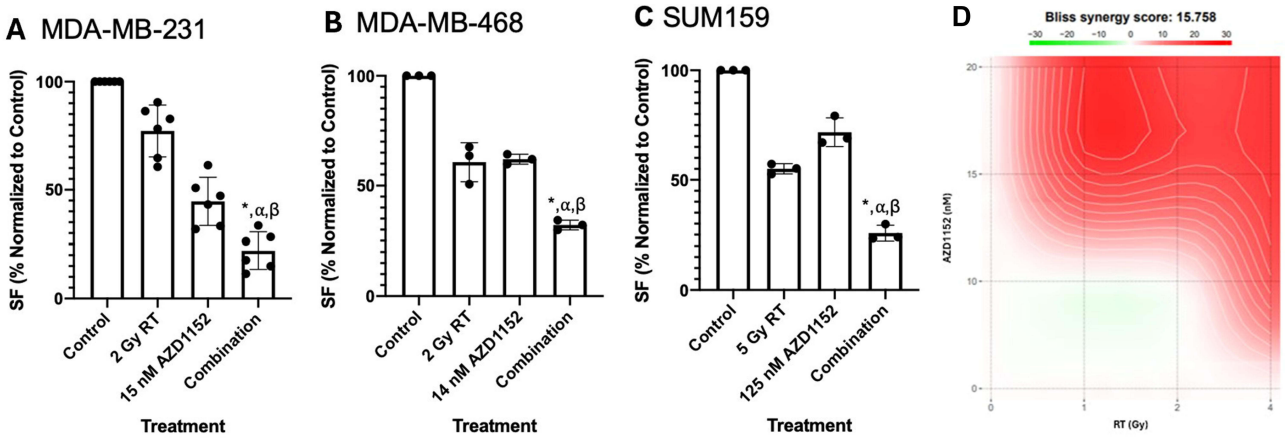

Figure 2 Effects of AZD1152 in combination with RT in TNBC cell lines. Combination treatment of (**A**) MDA-MB-231; (**B**) MDA-MB-468; (**C**) SUM159 cells with a single concentration of AZD1152 and a single dose of RT. Treatment with RT or AZD1152 alone results in reduced colony formation with further significant reduction of proliferation by a combination treatment relative to single agent treatment ($p \leq 0.05$ compared to control (*), RT only ($^{\alpha}$) or ($^{\beta}$) AZD1152 only treatment); (**D**) Synergy plot using various concentrations of AZD1152 and doses of RT in MDA-MB-231 cells using SynergyFinder, where the intensity of red indicates a higher degree of synergy (n = 3).
Abbreviation: SF, Surviving Fraction.

treatment resulted in a 70.6 ± 3.7% decrease in CF compared to control ($p \leq 0.05$). This translated to a 2.8- and 1.8-fold decrease in CF with the combination treatment compared to RT or AZD1152 only treatments respectively. In MDA-MB -468 (Figure 2B), single agent treatment with AZD1152 resulted in a 38.0% (SD = 2.2%) decrease in CF; 2 Gy of RT reduced CF by 39.3 ± 8.8%, while simultaneous combination treatment resulted in a 67.9 ± 2.2% decrease in CF compared to control ($p \leq 0.05$). This translated to a 1.9- and 1.9-fold decrease in CF with the combination treatment compared to RT or AZD1152 only treatments respectively. In SUM-159 (Figure 2C), single agent treatment with AZD1152 resulted in a 28.3% (SD = 6.6%) decrease in CF; 5 Gy of RT reduced CF by 45.0 ± 2.3%, while simultaneous combination treatment resulted in a 74.3 ± 3.6% decrease in CF compared to control ($p \leq 0.05$). This translated to a 2.2- and 2.8-fold decrease in CF with the combination treatment compared to RT or AZD1152 only treatments respectively. To confirm synergistic effect of the combination, we investigated dose response matrices of different concentrations of the drug and doses of RT using the CFA (N = 3) in MDA-MB-231 cells. The analysis of the data using the SynergyFinder software suggested synergy (Bliss score of 15.8) between the drug and RT in providing an antiproliferative effect in TNBC cell lines (Figure 2D).

Discussion

Targeting the axis of control of genomic stability appears to be a promising avenue for enhancing anticancer effects of RT. One of the promising targets for development of novel therapies in cancer is AURKB. It is localized to the centromeres and microtubules and is involved in the processes of chromosome alignment, kinetochore orientation and cytokinesis.[22] AURKB is often aberrantly expressed in breast cancer[26] and, if dysregulated, has been shown to induce genomic instability.[17] AURKB inhibition exacerbates genomic instability by targeting the microtubules or microtubule-organizing centres.[27] Inhibition of AURKB by AZD1152 has been shown to induce mitotic catastrophe (polyploidy, multinucleation and micronuclei formation) and sensitize cancer cells to RT.[20–22,28] RT itself is known to induce genomic instability.[7,10,11] Compounds that target proteins controlling genomic stability might enhance effects of RT and help in overcoming radioresistance. Hence, we investigated if the combination of AURKB inhibition with RT could further enhance anti-cancer effects of RT in TNBC.

In the current study, we assessed effects of the AURKB inhibitor AZD1152 in combination with RT in TNBC. We show that AZD1152 leads to a decrease in TNBC cell proliferation in various cell lines in vitro. Moreover, we observed that the combination of the drug and RT significantly decreases breast cancer cell proliferation compared to a single agent treatment. Our data are in agreement with the previously published reports in other cancer types. AZD1152 has been shown to enhance radiosensitivity and counteraction of radioresistance in colon,[21] lung,[22,28] gynecological [29] and androgen-resistant prostate cancer[20] cells. In non-small cell lung carcinoma cells, low concentration AZD1152 treatment during irradiation affected repopulation during RT.[28] These findings suggest that concomitant AURKB inhibition and RT may be a promising strategy for fast repopulating tumors, such as TNBC. This is an important observation, since in clinical trials in myeloid malignancies and solid tumours, while showing promising efficacy, AZD1152 (Barasertib), induced dose-limiting myelotoxicity limiting its subsequent clinical development.[18,30–32] Hence, combining low dose AURKB with RT might provide promising results in terms of decreasing drug toxicity, increasing its efficacy through RT-mediated chemosensitization and increasing RT efficacy. These multimodality treatment approaches are emphasized as a promising avenue for clinical development[8,9] and under investigation in clinical trials in patients with TNBC.[33–35]

Overall, this study confirms that inhibition of the AURKB axis is a promising strategy for therapeutic development, including multimodality treatment strategies to enhance sensitivity to and anticancer effects of RT in TNBC. Several non-specific or pan-aurora kinase inhibitors have also been investigated in Phase 1 and 2 clinical trials with limited clinical activity reported.[36–39] However selective AURKB inhibitors, such as AZD1152, show clinical promise as anticancer agents.[17] Clinical use of AZD1152 is being investigated with a limiting factor for clinical application being myelotoxicity. AZD1152 is a pro-drug of the highly potent and selective AURKB inhibitor AZD2811 and novel avenues are being explored to improve efficacy and tolerability of AZD2811, such as use of nanoparticles for drug delivery.[32,40–42]

The limitations of this study include the use of immortalized cancer cells that might not well represent the heterogeneity of TNBC and the lack of in vivo data regarding this combination. Future studies utilizing patient-derived in vitro and in vivo models would help to better capture the heterogeneity observed in TNBC patients and would better recapitulate patient responses to this combination. This manuscript provides the first evidence for the potential role of combining AURKB inhibition with RT in the treatment of TNBC using immortalized human cancer cell lines. Further translational studies of the combination treatments with AURKB inhibition and RT are warranted to facilitate development of clinical trials and new treatments in TNBC. This multimodality treatment strategy might be found to be useful in various clinical scenarios, such as in the neoadjuvant setting where surgical removal of the primary tumor might be facilitated by enhancing its response and making it smaller; or in a metastatic setting where the combination of this radiosensitizing drug with radiation would provide better control of the metastatic deposits.

Conclusion

In conclusion, AURKB inhibition appears to be a promising target for the treatment of TNBC as a single agent or in combination with RT. Further translational and clinical studies of AZD1152 and its analogues would shed light on the clinical application of AURKB inhibition in the treatment of TNBC as a single agent or in combination with other chemo and radiotherapeutic approaches.

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Disclosure

The authors declare no conflicts of interest in this work.

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