The potential sensitizing action of pioglitazone on cisplatin in triple negative breast cancer.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a type of BC known for its aggressive course, ability to evade apoptosis and resistant to chemotherapeutic drugs including cisplatin (Cis). Peroxisome proliferator-activated receptors gamma (PPAR-γ) are important regulators of apoptotic proteins. It has been found that PPAR-γ agonists mediate a downregulation of Bcl-2 and upregulation of BAD/BAX, among others. There is also evidence that PPAR-γ activation resulted in inhibition of breast tumor growth. Indeed, PPAR-γ expression in TNBC is downregulated compared to other BC.

OBJECTIVES

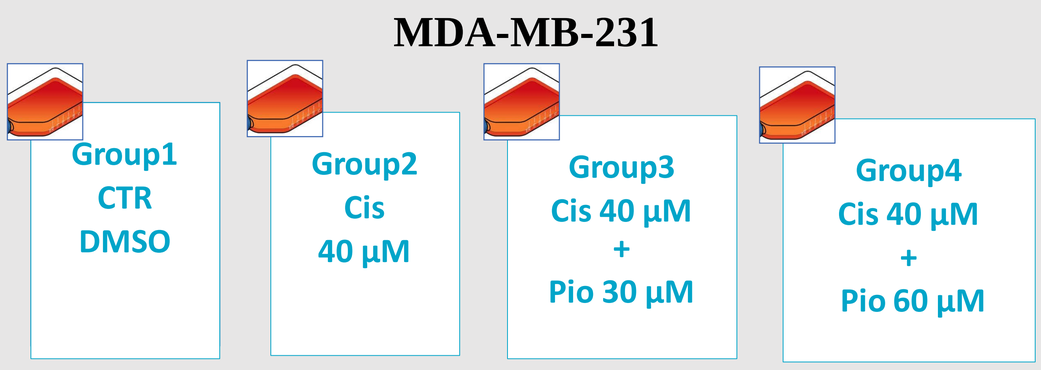
This project aims to:

- Study the synergistic effect of Pioglitazone (Pio) on Cis induced cytotoxicity.
- Investigate the molecular effect of cisplatin/pioglitazone combination on the expression of several apoptotic markers.

METHODS

CELLS AND CELL CULTURE: MDA-MB-231 (human breast cancer) cells were cultured with RPMI medium supplemented with 10% fetal bovine serum (FBS) and 1% of Penicillin-Streptomycin in a T-75 tissue culture flask and maintained under 5% CO2 at 37°C and 95% of relative humidity.

STUDY DESIGN:



CELL VIABILITY ASSAY: MTT assay. Methyl thiazolyl tetrazolium (MTT) assay was used to assess cell viability. The median inhibitory concentration (IC50) was calculated by a non-linear regression of the plot using GraphPad Prism.

IMMUNOBLOTTING ANALYSIS: At the molecular level, the treated cells were subjected to immunoblotting analysis to investigate the differences in the expression level of several apoptotic markers.

RESULTS

- Combining Cis (40 µM) with Pio (30 or 60 µM) for 72 hours results in a dose-dependent decrease in cell viability, indicating the possible synergistic effect of Pio on Cis induced cytotoxicity (figure 1).
- Next, we sought to investigate the impact of the combination therapy at a molecular level. Interestingly, expression of Bcl-2, an antiapoptotic marker, decreased in cells treated with the combination, while cleaved-PARP and -caspase-9 were upregulated. (figure 2).

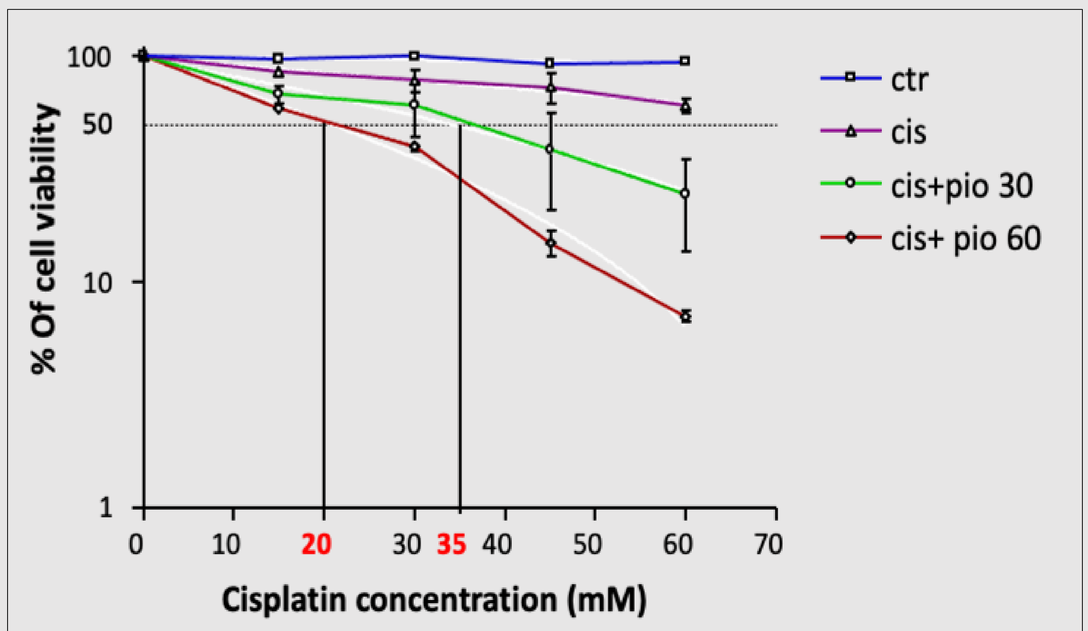


Figure 1. Pioglitazone augments the cytotoxic effect of cisplatin.
The cytotoxicity was determined based on MDA-MB-231 cell viability after treatment with either cisplatin at different doses (20, 40, 60 or 80 µM) or the combination of cisplatin, at these doses, with 30 or 60 µM pioglitazone for 72 h using the MTT test. The arrows indicate the LC_{50} for each treatment group. The results are presented as mean ± SEM (n=3).

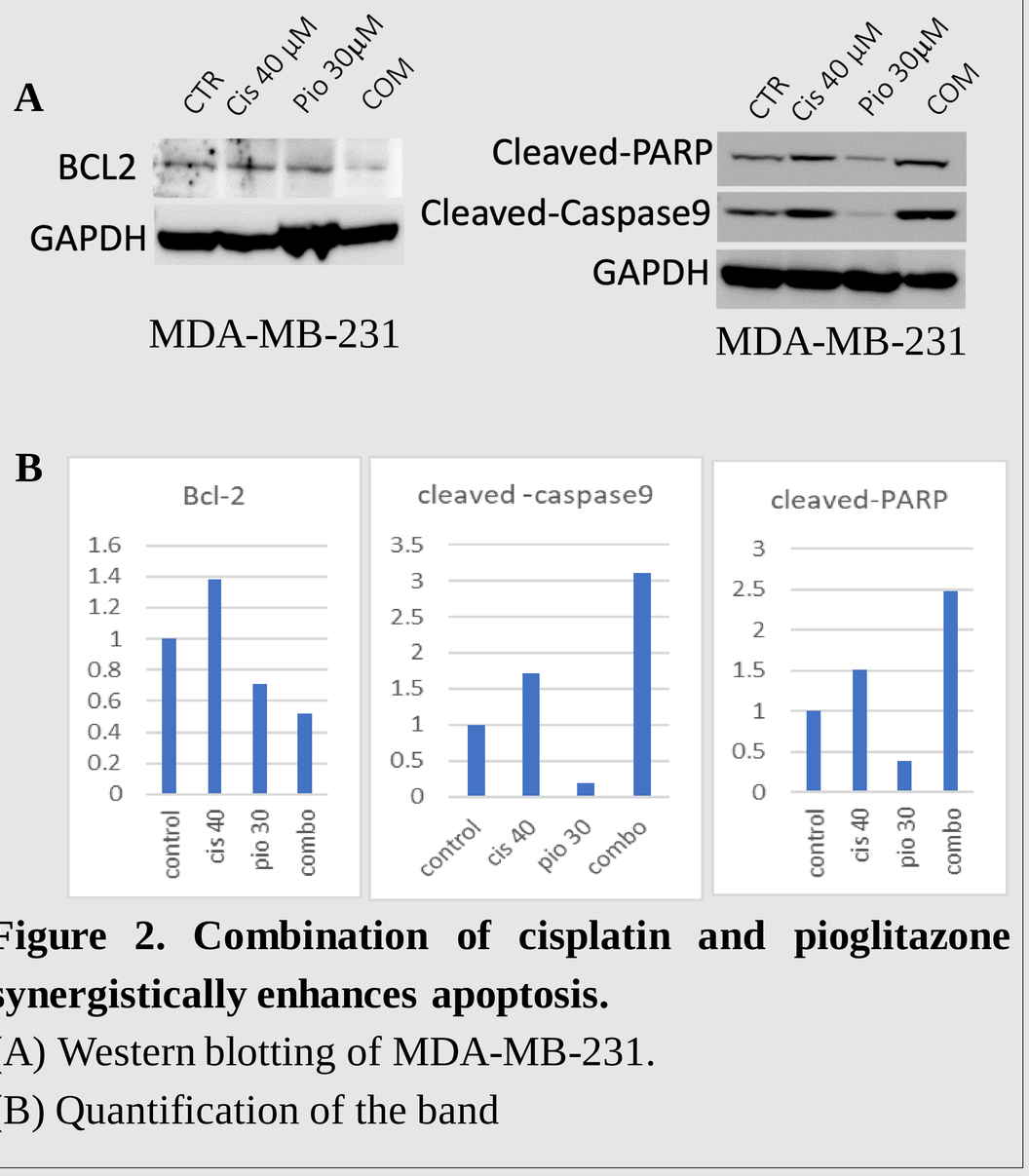


Figure 2. Combination of cisplatin and pioglitazone synergistically enhances apoptosis.
(A) Western blotting of MDA-MB-231.
(B) Quantification of the band

DISCUSSION & CONCLUSION

In conclusion these results provide a strong evidence for the favorable synergistic activity of Pio, a PPAR-γ agonist, with Cis as adjuvant therapeutic approach for TNBC.

REFERENCES

For references, please scan the QR Code: