Cureus

Theoretical Quantification of Cytotoxicity and Temporal Adaptive Response Induced by Very Low Dose X-irradiation in Beta-lapachone Resistant Prostate Cancer Cells

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Abstract

BACKGROUND: NQO1 is an intracellular phase II anti-oxidant enzyme. LNCaP prostate cancer cell line is known to be NQO1-deficient in contrast to PC3 cell line. LNCaP cells are therefore known to be more resistant to NQO1-dependent cytotoxic effects of beta-lapachone (β-lap), a promising bioreductive anticancer drug. Low doses of radiation have been shown to induce adaptive responses in normal and malignant cells. This could either lead to cell survival or cell death.

OBJECTIVES: The aim of this study was to theoretically quantify the effects of very low dose x-ray radiation (VLDR) at 20 mGy/hr. in LNCaP cells before and after treatment with β-lap.

METHODOLOGY: MTT assay was used to assess the cell viability and growth inhibition in cultured LNCaP and PC3 cells exposed to both VLDR and graded doses (1-7 μM) of β-lap singly or in combination. Light and phase contrast microscopy were used to check for apoptosis and autophagy. To assess induced adaptive response, period of time between priming with VLDR and treatment with doses of β-lap was varied from 1 to 24 hours. Modified median effect equation and CompuSyn software were used to analyse and determine the combination index and dose reduction index. Time-dependent change in ROS levels was also assessed by NBT assay after exposure to VLDR.

RESULT & CONCLUSION: The data revealed that initiation of adaptive responses following pre-exposure to VLDR and β-lap are time and dose-dependent.

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Theoretical Quantification of Cytotoxicity and Temporal Adaptive Response Induced by Very Low Dose X-irradiation in Beta-lapachone Resistant Prostate Cancer Cells

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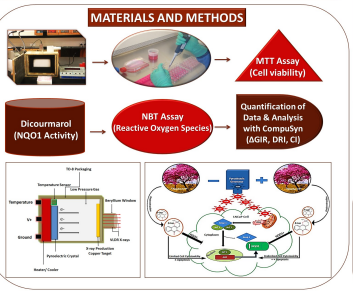
INTRODUCTION

NQO1 is an intracellular phase II anti-oxidant enzyme. LNCaP prostate cancer cell line is known to be NQO1-deficient in contrast to PC3 cell line [1]. LNCaP cells are therefore known to be more resistant to NQO1-dependent cytotoxic effects of beta-lapachone (β-lap or BL), a promising bioreductive anticancer drug [2]. Low doses of radiation have been shown to induce adaptive responses in both normal and malignant cells [3]. This could either lead to cell survival or cell death.

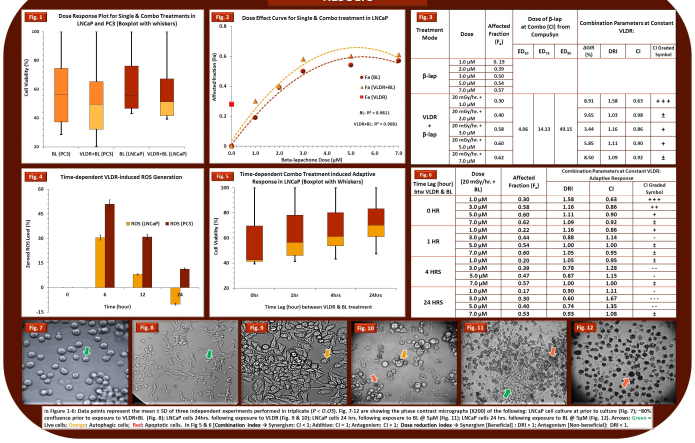
OBJECTIVES

- To assess and compare the cytotoxic effects of very low dose X-ray radiation (VLDR; (20mGy/hr.) & β-lap in both LNCaP and PC3 prostate cancer cell lines.
- To theoretically quantify the effects and temporal adaptive responses to VLDR in beta-lapachone resistant LNCaP cells.

MATERIALS AND METHODS



RESULTS



DISCUSSION & CONCLUSION

- LNCaP cells show dose- and time-dependent changes in adaptive stress responses to VLDR & BL as revealed by the change in DRI and/or CI values.
- The data suggest that VLDR induced an initial rise in the ROS levels, followed by increased generation of anti-oxidant enzymes such as NQO1 in LNCaP.
- In addition, data suggest that the major mode of cell death by this combination therapy are via Autophagy (VLDR) & Apoptosis (VLDR+BL).
- In conclusion, our results confirm that VLDR-induced NQO1 levels contribute to LNCaP cell death by enhancing the phytotherapeutic effects of β-lap.
- The result from this study revealed the priming effect of VLDR on β-lap resistant (NQO1-deficient) prostate cancer, thus offering a potential synergistic adjuvant therapy.

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