PHENETHYLISOTHIOCYANATE: ROLE IN ENHANCING PLATINUM ACCUMULATION IN CERVICAL CANCER

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ABSTRACT

Acquired cisplatin resistance stymies cervical cancer therapy. Principally, an upregulated oncogenic PI3K/Akt signalling axis overexpresses cisplatin-exporters (MRP2, ATP7A, ATP7B) and hyperactivates prosurvival-effectors such as NFκB and IAPs in cervical cancer cells to reduce intracellular cisplatin accumulation for establishment of a chemoresistant phenotype. It is a manifestation of activated prosurvival signalling driven drug-efflux and apoptosis evasion upon cisplatin encounter. In our study, PI3K/Akt axis in cisplatin-resistant cervical cancer scenario was challenged by Phenethylisothiocyanate (PEITC) which is a natural isothiocyanate derived from cruciferous vegetables for chemosensitization as well as for chemoenhancement. Herein, we made use of two pre-clinical models- $SiHa^R$, a cisplatin resistant sub-line of SiHa along with 3-methylcholanthrene (3MC) induced cervical cancer mice models for recording observation asserting the role of PEITC as a Resistance Modifying Agent (RMA).

$SiHa^R$ exhibiting higher MRP2, p-Akt^{Thr308}, NFκB, XIAP and survivin expressions espoused compromised cisplatin retention capacity which significantly improved following PEITC treatment. In fact, combination treatments with PEITC and CDDP synergized the drug retention potentials of $SiHa^R$ in comparison to SiHa. We experimentally confirmed that MRP2 enriched $SiHa^R$ favored PEITC uptake as its accumulation rates positively-correlated with its MRP2 expressions. PEITC treatment in $SiHa^R$ for 3h prior to cisplatin exposure revived intracellular platinum levels, reduced free GSH levels, generated greater ROS and altered mitochondrial membrane-potential compared to the cisplatin sensitive SiHa. Western blot, and immunofluorescence results indicated that PEITC successfully downregulated MRP2 in addition to suppressing p-Akt^{Thr308}, XIAP, survivin and NFκB expressions. In invasive cervical cancer bearing mice, priming with PEITC prior to treatment with cisplatin remediated cervical histology as well as cytopathology. Additionally, tumor regression along with threshold levels of ROS, RNS and iNOS induction was achieved along concurrent chemocycles of PEITC and CDDP for 2 weeks. This suggested PEITC as a potential cisplatin sensitizer among resistant cervical cancer scenario which established its candidature for Phase I clinical trial in days to come.

Keywords: PEITC, chemosensitization, cisplatin-resistance, MRP2, PI3K/Akt, prosurvival signalling.

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