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Isoquinolinequinone *N*-Oxides as Promising Antitumor Compounds in Pancreatic Cancer Cell Lines

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) represents the 12th most commonly diagnosed malignancy worldwide and the sixth leading cause of cancer-related mortality, with more than 500,000 new cases and nearly 470,000 deaths recorded in 2022 [1]. Its poor prognosis is largely driven by intrinsic and acquired drug resistance, leading to mortality rates above 90%. Current treatment mainly relies on gemcitabine, either alone or in combination with paclitaxel [2,3], highlighting the urgent need for novel anticancer agents, particularly those able to overcome chemoresistance. Recently, isoquinolinequinone (IQQ) *N*-oxides have shown promising antitumor activity in pairs of sensitive and multidrug-resistant (MDR) lung and colorectal cancer cell models [4,5]. **Objective:** This study aimed to evaluate the antitumor effects of IQQ *N*-oxides in several PDAC models, including a sensitive and resistant PDAC cell line. **Methods:** MiaPaCa-2, Capan-1, BxPC-3, Panc-1, and the resistant Panc-1-CDR PDAC cells were treated with different concentrations of IQQ *N*-oxides (RK1-RK9) or gemcitabine for 48 h. Cell viability was assessed by SRB assay, while long-term clonogenic potential was determined by colony formation assay (2 or 6 days). Anti-migratory effects were evaluated using a wound healing assay over 48 h. **Results:** RK2 and RK3 emerged as the most potent derivatives, with GI_{50} values ranging from 0.80 to 2.35 µM across multiple cell lines. Both compounds remained effective in the gemcitabine-resistant Panc-1-CDR model, with GI_{50} values of 1.41 and 1.14 µM, respectively. Moreover, the clonogenic assay showed a marked concentration and time-dependent reduction in colony formation, with near-complete inhibition by day 6 when Panc-1 cells were treated with RK2 and RK3. Additionally, treatment with RK2 and RK3 significantly impaired cell migration at 1µM concentration, limiting wound closure to 60% and 51%, respectively, after 48h (compared to 80% in control cells). **Conclusions:** The IQQ *N*-oxide derivatives, RK2 and RK3, effectively reduced PDAC cell growth, including in a gemcitabine-resistant PDAC cell line, and suppressed key malignant traits such as self-renewal and migration, supporting their potential as promising therapeutic leads for PDAC.

Keywords: chemoresistance; isoquinolinequinone *N*-oxides; pancreatic cancer

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