Synergistic effect of FOXM1 inhibitor on 5-FU cytotoxicity in cholangiocarcinoma cell lines

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Abstract: Cholangiocarcinoma (CCA), a bile duct malignancy, occurs both intra- and extra-hepatic ducts. Prognosis of CCA is very poor due to the difficulties in diagnosis and advanced stage tumor when it is diagnosed. The problem in the management of the advanced CCA patients is poor response to the available chemotherapy. 5-Fluorouracil (5-FU) is a common chemo-drug for CCA treatment; however, its efficacy is reduced according to the drug resistance developed in CCA cells. Forkhead box M1 (FOXM1) is upregulated in human CCA tissues and involved with several chemoresistance mechanisms. FOXM1 is a directly transcriptional factor for Thymidylate synthase (TS), the target of 5-FU, that is necessary for DNA synthesis. Suppression of FOXM1 together with 5-FU treatment might reduce 5-FU chemoresistance in CCA. The aim of this study is to demonstrate the enhancing effect of FOXM1 inhibitor, Siomycin A (SioA), on cytotoxicity of 5-FU in CCA cell lines. The proliferation of CCA cell treated with SioA or 5-FU alone was performed. The effect of 5-FU in combination with SioA on CCA cell proliferation was measured as the combination index and dose reduction index using Compusyn software. SioA combined with 5-FU exhibited a synergistic effect. SioA decreased 5-FU resistance by suppressing TS expression in the resistant cells. This study suggested that the combination of FOXM1 inhibitor with 5-FU might be a strategy to overcome 5-FU resistance in CCA.

Keywords: Bile duct cancer, FOXM1, Siomycin A, 5-Florouracil, Thymidylate synthase, Synergistic effect, Drug combination, combination index

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