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Telotristat Ethyl Augments Cytotoxic Chemotherapy Response in Preclinical Tumor Models

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BACKGROUND: Cholangiocarcinoma (CCA) has a poor prognosis with a 5-year survival rate of 5-15%. Gemcitabine plus cisplatin (GemCis) remains the standard therapy for CCA. Nab-paclitaxel (NPT) is an approved treatment for breast, lung and pancreatic cancer. Increased serotonin levels have been observed in CCA that has protumorigenic activity. The therapeutic efficacy of telotristat ethyl (TE), an inhibitor of serotonin biosynthesis, was determined in combination with cytotoxic therapy in preclinical CCA models.

METHODS: Animal survival studies were performed using human CCA intrahepatic CCLP-1 cells in the peritoneal dissemination model in NOD/SCID mice. Tumor growth studies were performed in subcutaneous xenografts using CCA intrahepatic CCLP-1 cells and extrahepatic TFK-1 cells in NOD/SCID mice.

RESULTS: Compared with controls, animal survival was only slightly increased by TE (11%) or GemCis (9%) while NPT led to a greater extension (60%). Importantly, the combination of TE with GemCis or NPT demonstrated an increase in animal survival: GemCis+TE (26%) and NPT+TE (68%). In intrahepatic CCLP-1 subcutaneous xenografts, compared to controls, tumor growth inhibition was observed by TE (53%), GemCis (53%) or NPT (69%). Importantly, combinations of TE with cytotoxic agents exhibited an additive effect on tumor growth inhibition, GemCis+TE (85%) and NPT+TE (90%). In extrahepatic TFK-1 subcutaneous xenografts, TE caused a similar effect as in intrahepatic CCLP-1 xenografts while GemCis or NPT effects were less pronounced.

In this setting, compared to controls, tumor growth inhibition was 51% by TE, 37% by GemCis (37%) and 56% by NPT. Again, the addition of TE to chemotherapy exhibited an additive tumor growth inhibition response, GemCis+TE (67%) and NPT+TE (74%).

CONCLUSION: TE showed antitumor efficacy, and it also augmented antitumor effects of GemCis or NPT chemotherapy suggesting that this combination has the potential for improving clinical CCA therapy.

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