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Rigosertib as a radio-sensitizer for concurrent chemo-radiation treatment of cholangiocarcinoma (CCA): a comparative study *in vitro*

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Cholangiocarcinoma (CCA) remains a therapeutic challenge. The small-molecule Rigosertib can selectively synchronize cancer cells to G2/M phase improving the efficacy of radiation. In our study, we evaluated *in vitro* Rigosertib (gifted by Onconova Therapeutics Inc) effects on two human CCA cell lines: EGI-1 and TFK-1. Rigosertib was compared with Gemcitabine (GEM) and 5-Fluorouracil (5-FU), two antineoplastic and radio-sensitizer agents used in the treatment of CCA.

Rigosertib impaired cell viability (evaluated by Tripan-blue vital count) in both cell lines in a dose- and time-dependent manner (IC_{50} of 100nM at 24h). GEM and 5-FU had a IC_{50} of 30μM and 7μM after 24h, respectively. Cell migration and invasion tests was performed by scratch wound healing and Boyden chamber assay respectively. Rigosertib caused a 50% inhibition of the EGI-1 cell migration (10μM) and invasion (100nM), while the inhibitory effects on TFK-1 cells were observed with doses of 100μM and 10μM, respectively. GEM 30μM and 5-FU 7μM had no effect on cell migration and invasion. Evaluation of cell cycle by FACS cytometry showed a G2/M arrest in both cell lines after Rigosertib 100nM for 24h. Radio-sensitizing test was performed by clonogenic survival assay after irradiation. 24h Rigosertib pre-treatment (100nM for EG-1 and 1 μM for TFK-1) when followed by 2, 4 or 6 Gy irradiation, reduced survival in both CAA cell lines when compared with radiation alone. The Rigosertib radio-sensitizer effect was similar to that seen after GEM or 5-FU 24 pre-treatment both plus irradiation. However, 48h Rigosertib pre-treatment was more effective than radiation alone as well as GEM for 48h.

Our study highlights the preliminary but promising preclinical activity of Rigosertib both as antitumoral and as a radio-sensitizer agent in CCA and provides a background for further investigations.

Keywords

Cholangiocarcinoma, Rigosertib, radio-sensitizer, antitumoral effects