The Mechanism of Action of Sorafenib in Desmoid-type Fibromatosis

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Background Desmoid-type fibromatosis (DTF) is a rare, soft tissue tumor arising in musculoaponeurotic structures, with a highly unpredictable clinical course. The choice of appropriate treatment strategies can be challenging. Results of recent studies showed that sorafenib can slow down the progression of DTF, and is therefore a promising therapeutic option for progressive, refractory or symptomatic desmoid tumors. However, the underlying mechanisms by which sorafenib affects DTF cells are still not completely understood. Here, we investigated the cellular effects of sorafenib on DTF cells lines.

Materials and methods Two DTF primary cell-cultures (Erasmus MC) and one DTF cell-line (kind gift Dr. B. Alman, Duke University) harboring the CTNNB1 S45F and T41A mutations were exposed to increasing concentrations of sorafenib (2.5,10 and 20 μM) with or without ferroptosis- (Ferrostatin-1), apoptosis- (Z-VAD-fmk) and necrosis- (Necrostatine-1) inhibitors. After 72 hours of drug exposure, cell viability was determined using the SRB assay.

Results We found that exposure to sorafenib (20 μM) resulted in an 80% reduction of cell viability. The effect on desmoid cell viability was less profound with a sorafenib concentration of 10 μM, whereas 2.5 μM sorafenib did not result in a decrease in cell viability. For all concentrations of sorafenib, the decrease in cell viability was not rescued by the inhibitors of ferroptosis, apoptosis and necrosis. No differences were found in response to sorafenib between S45F and T41A mutant DTF cells.

Conclusion Our findings suggest that sorafenib is able to decrease cell viability of DTF cells. This cytotoxic effect does not seem to be caused by the induction of ferroptosis, apoptosis or necrosis. Moreover, response to sorafenib did not differ between CTNNB1 S45F and T41A mutant cells. Our observations are in contrast with a recently published study (Braggio et al., 2019) describing the induction of apoptosis as mechanism of action from sorafenib in DTF cells, with different responses of the mutational subtypes (S45F and T41A). Additional experiments are required to further elucidate the mechanism by which sorafenib causes its cytotoxic effect in DTF cells.

Future prospective We will further investigate the cellular mechanisms by which sorafenib causes a decrease in DTF cell viability, and whether its cytotoxic effect and underlying mechanism differs between mutational subtypes. To this end, we want to quantitatively examine characteristics of ferroptosis, apoptosis, and necrosis as

well as the cell cycle progression using additional methodologies. Special attention will be given to assess whether sorafenib induces autophagy and which cellular pathways are affected.