Quizartinib (AC220) Reverses ABCB1- and ABCG2-Mediated Multidrug Resistance

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Multidrug resistance (MDR) is a major obstacle to successful chemotherapy. The main cause of MDR is the increased drug efflux by ABC transporters. AC220 is a potent and selective inhibitor of fms-like tyrosine kinase 3 (FLT3). Many tyrosine kinase inhibitors have shown to reverse ABC transporter mediated MDR. The high toxicity of previous modulators of ABC transporters requires the identification of potent and clinically safe modulators. Since AC220 is a potent TKI, this study aimed to determine the effect of AC220 on ABC transporter mediated MDR in multiple resistant cancer cell lines. The MTT assay showed that .75 and 3 μM for AC220 is a less toxic concentration for normal as well as sensitive cancer cells. AC220 at 3 μM showed a significant reversal of MDR mediated by ABCB1 and ABCG2 in KB-C2, H460/Mx20, HEK293/482-R2, and HEK293/482-T7 cell lines. Additionally, AC220 has shown to increase the intracellular accumulation of [3H]-Mitoxantrone in HEK293/482-R2 cells by more than 50% and in HEK293/482-T7 cells by more than 38%. AC220 decreased the efflux of [3H]-Mitoxantrone in HEK293/482-T7 cells by 70% and in HEK293/482-T7 cells by more than 55%. Docking simulations confirmed the molecular interaction between homology models of human ABC transporters and AC220. AC220 may be combined with other conventional anti-cancer drugs for successful chemotherapy. AC220 may decrease the expenditure of pharmaceutical companies developing anti-cancer agents that are non-substrates of ABC transporters. Future experiments will elucidate AC220's mechanism of action and its in vivo effect using tumor xenograft nude mice.

Awards Won:

Third Award of $1,000