In silico drug screening for taxane-resistant prostate cancer using bioinformatic analysis.

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Introduction: Because CBZ-resistant CRPC has an extremely poor prognosis, establishment of a novel treatment for CBZ-resistant CRPC is greatly needed. The aim of this study was to explore drugs targeting the CBZ-resistance related genetic network by bioinformatic analysis and testing the antitumor effects of CBZ for resistant CRPC.

Methods: Two CRPC cell lines, DU145 and PC3, and two CBZ-resistant cell lines were used in this study. We incubated the cell lines with gradually increasing concentrations of CBZ to establish CBZ-resistant cell lines. We performed screening tests for candidate drugs to inhibit the genetic network in CBZ-resistant CRPC using in silico analysis, and identified a candidate drug, KWH-05. The antitumor effect of KWH-05 for CBZ-resistant cell lines was determined using mice xenograft tumor models.

Results: We incubated DU145 and PC3CR cells with gradually increasing concentrations of CBZ for 2 years and established the CBZ-resistant cell lines, DU145CR and PC3CR. These CBZ-resistant cell lines underwent cell division with 3 nM CBZ. Cell cycle analysis demonstrated DU145CR and PC3CR had resistance to G2/M arrest induced by CBZ. Microarray analysis revealed gene clusters related to cell division were up-regulated in DU145CR and PC3CR. Next, we tested the anti-tumor effect of the candidate drug KWH-05 for overcoming CBZ-resistance. KWH-05 treatment had an anti-tumor effect in CBZ-resistant cell lines. Quantitative PCR revealed that KWH-05 down-regulated mRNA expression of the AURKB and KIF20A, which regulates G2/M transition. AURKB / KIF20A inhibitors or genetic knockdown of AURKB or KIF20A suppressed cell proliferation of DU145CR and PC3CR. We tested the efficacy of KHO031 for CBZ resistance in mice xenograft models. KWH-05 inhibited xenograft tumor growth in monotherapy. In addition, KWH-05 and CBZ had a synergic effect on DU145CR and PC3CR xenograft tumors. These results suggest that KWH-05 has potential for reprogramming CBZ-resistant CRPC.

Conclusions: Targeting the G2/M regulation mechanism with KWH-05 can overcome CBZ resistance in CRPC.