A Preclinical Study on Wee1 Inhibitors for Enhancing Chemotherapy Response in Bladder Cancer

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Bladder cancer is the fourth most common cancer among men, affecting more than 80,000 people in the United States every year. Cisplatin, a chemotherapy agent, is employed in the standard-of-care for patients with advanced bladder cancer. However, around 70% of patients are exposed to this toxic therapy without clinical benefit. Therefore, it is critical to develop a better strategy to improve the response rate in cisplatin-treated patients. Wee1 is a kinase that regulates the G2/M checkpoint, arresting the cell cycle. WEE1 expression is found to be increased in cisplatin-treated human bladder cancer cell line. Wee1 mRNA expression and clinical data are accessed through The Cancer Genome Atlas Program (TCGA), which remains publicly available. The data analysis in R shows that Wee1 expression is higher in patients with higher tumor stages ($p<0.001$). Also, patients with higher Wee1 expression have worse overall survival outcome than those with lower Wee1 expression ($p<0.01$). Wee1 inhibitors, Wee1i and PD0166285, are identified through literature research. The combined effects of Wee1i or PD0166285 with cisplatin show increased platinum cytotoxicity in bladder cancer cell lines. The combined treatment also enhances the expression of cleaved caspase-3, a biomarker for cell apoptosis. In summary, patients who have high Wee1 expression have poor clinical outcomes. Wee1 inhibitors exhibit synergistic effects with cisplatin in bladder cancer cell lines by increasing cytotoxicity and cell apoptosis. This study supports the notion that inhibition of Wee1 improves cisplatin-based chemotherapy response. It constitutes an innovative and promising therapeutic strategy for patients with bladder cancer.