Direct Targeting of the Cell cycle Regulator WEE1 is a Novel Therapeutic Approach for Neuroblastoma

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High-risk neuroblastoma (NB) is a solid pediatric tumor that develops from the extracranial sympathetic nervous system. Despite recent advances in therapeutic regimens of dose-intensive chemotherapies, radiation, and surgery NB often relapses as a metastatic and drug-resistant tumor. These issues further mandate the identification and development of novel therapeutic approaches for NB treatment. Cell cycle regulators, Cdk1 in combination with cyclin B1, and Cdk2 with cyclin E regulate the G2/M checkpoint and G1/S checkpoint respectively, to obstruct the cells from proceeding into mitosis with genomic DNA damage. Wee1, a tyrosine kinase, regulates the phosphorylation of Cdk1 and Cdk2 at tyrosine residues in response to DNA damage, making them inactive. Previous studies have reported high expression of Wee1 in NB patients and associate Wee1 with an overall poor NB prognosis. Inhibition of Wee1 obstructs the Cdk1 and Cdk2 activation and is no more reliant on an intact G2/M checkpoint for survival. In the present study, we analyzed multiple NB patient datasets and found that Wee1 expression is strongly correlated with poor overall survival of NB patients. Further, we used a specific small molecule Wee1 inhibitor in NB cells and observed that Wee1 inhibition significantly and in a dose-dependent manner inhibits NB proliferation and colony formation capacity in both MYCN-amplified and MYCN non-amplified NB cells. Further, Wee1 inhibition significantly induces apoptosis up to 3-fold in different NB cells in contrast to control treatments. Additionally, we used NB 3D spheroid models that mimic in vivo NB tumor growth and found that Wee1 inhibition significantly and in a dose-dependent manner inhibits 3D spheroid growth and volume up to 2.3-fold in contrast to control treatments. Additionally, and as expected, inhibition of Wee1 significantly inhibits NB cell cycle progression by inhibiting cell cycle S phase and blocking G2/M checkpoint in different NB cell lines. Further, the Wee1 inhibition inhibits the gene expression levels of different cell cycle-related genes in NB cells such as CDK1, CDK2, CCNB1, CHK2, and BCL-2. Overall, our data suggest that inhibition of the cell cycle regulator Wee1 is an effective therapeutic approach for NB. Further combining Wee1 inhibitors with current therapies will pave the way for developing effective targeted therapeutic approaches for NB patients.

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