Exploring the In Vitro Effects of PARP-1 Inhibition on Neuroblastoma Tumors

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Introduction: Neuroblastoma is one of the most common extracranial tumors found in juveniles. Because of its generalized symptoms and the fact that most cases develop during infancy, it is often diagnosed at a late stage where common treatments are less effective. In Neuroblastoma, MYC-N genomic amplification and segmental chromosomal alterations are associated with greater disease progression and poorer clinical outcome. Segmental alterations are the greatest predictor of relapse and are attributed to erroneous repair of chromosomal breaks through a low fidelity alternative-non homologous end joining (alt-NHEJ) repair pathway. Interestingly, in tumors using this pathway, repair enzymes present in the alt-NHEJ are upregulated while classical NHEJ repair enzymes are down regulated. Poly ADP Ribose Polymerase-1 (PARP-1) plays a critical role in the alt-NHEJ pathway by using N-terminus zinc fingers to detect breaks in the genome and then signaling other enzymes that consequently bind to, and repair, the single strand breakages (SSB). On this basis, we sought to test the hypothesis that inhibiting PARP-1 in vitro would reduce the comparative survivability of high-risk neuroblastoma cells.

Methods & Results: We used cell lines: SKNSH, IMR5, BE2, BE2C, NB1691, NLF, SY5Y due to their characterization of high-risk neuroblastoma and performed growth inhibition assays using four PARP-1 inhibitors: talazoparib, niraparib, olaparib, and veliparib. Our data revealed that although all the cell lines studied showed clear responses to PARP-1 inhibition (PARPi), there was clear variation in which inhibitors worked best. The cell lines showed greatest sensitivity to talazoparib followed by niraparib, olaparib, and then veliparib.

Conclusion: From our data we can definitively conclude that there is a clear differential in vitro response to PARP-1 inhibitors. Additionally, we noted that cells with a P53 mutation were often less sensitive to PARPi, although more research is necessary to definitively claim that. In future studies, we hope to look at PARP-1 expression and compare that to relative PARPi sensitivity in neuroblastoma cells. Additionally, radioligand binding studies may be useful in further understanding the interaction between PARP-1 and its inhibitors.