AMXT-1501, a novel polyamine transport inhibitor, synergizes with DFMO in inhibiting neuroblastoma cell proliferation by targeting both ornithine decarboxylase and polyamine transport

Katherine Samal[1], Ping Zhao, Ann Kendzicky, Lisette P Yco, Heather McClung, Eugene Gerner, Mark Burns, André S Bachmann, Giselle Sholler
Affiliations Expand

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Abstract

Neuroblastoma (NB) is associated with MYCN oncogene amplification occurring in approximately 30% of NBs and is associated with poor prognosis. MYCN is linked to a number of genes including ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine biosynthesis. ODC expression is elevated in many forms of cancer including NB. Alpha-difluoromethylornithine (DFMO), an ODC inhibitor, is currently being used in a Phase I clinical trial for treatment of NB. However, cancer cells treated with DFMO may overcome their polyamine depletion by the uptake of polyamines from extracellular sources. A novel polyamine transport inhibitor, AMXT-1501, has not yet been tested in NB. We propose that inhibiting ODC with DFMO, coupled with polyamine transport inhibition by AMXT-1501 will result in enhanced NB growth inhibition. Single and combination drug treatments were conducted on three NB cell lines. DFMO IC50 values ranged from 20.76 to 33.3 mM, and AMXT-1501 IC50 values ranged from 14.13 to 17.72 μM in NB. The combination treatment resulted in hypophosphorylation of retinoblastoma protein (Rb), suggesting growth inhibition via G1 cell cycle arrest. Increased expression of cleaved PARP and cleaved caspase 3 in combination-treated cells starting at 48 hr suggested apoptosis. The combination treatment depleted intracellular polyamine pools and decreased intracellular ATP, further verifying growth inhibition. Given

the current lack of effective therapies for patients with relapsed/refractory NB and the preclinical effectiveness of DFMO with AMXT-1501, this combination treatment provides promising preclinical results. DFMO and AMXT-1501 may be a potential new therapy for children with NB.

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