PRECLINICAL STUDIES ON THE INHIBITION OF PIM-1 BY SGI-1776 AS AN EFFECTIVE TARGETED THERAPEUTIC FOR HIGH RISK PEDIATRIC LEUKEMIA

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Abstract

Internal tandem duplications (FLT3/ITDs) in childhood leukemia lead to constitutive receptor activation and an aggressive malignant phenotype. Because of the powerful proliferative signaling, FLT-3 and its co-regulators have been considered to be effective targets for therapeutics. The Pim-1 serine/threonine kinases are downstream effectors of many growth factor signaling pathways. Recent studies have shown the association of Pim-1 in leukemia cells with FLT-3 ITDs and that may be involved in the growth and survival of these cells. Although a number of small molecule Pim-1 inhibitors have been described, comprehensive preclinical studies to evaluate the activity of these agents against pediatric leukemia are not available. Furthermore, there is a great need to define the biological correlates of Pim-1 inhibition in leukemia cells and identify effective drug combinations to enhance the efficacy of future clinical trials. In this report we examined the in vitro cytotoxicity and target modulation capabilities of the PIM-1 inhibitor SGI-17776 against a panel of pediatric leukemia derived cell lines and primary leukemia specimens (n=9). Our studies showed IC50 values varied significantly based on FLT-3 ITD (range 0.0032 μM – 10 μM, Mean = 4 μM). The two FLT-3 ITD cells showed significantly lower IC50 values (Mean = 0.03 μM). Interestingly, however, no significant differences were noted in the expression of PIM-1 among the cells tested. Next we evaluated the utility of SGI-17776 in drug combination studies with a panel of novel and conventional drugs. Our results identified a number of potential agents including the FLT-3 inhibitor crenolanib that showed additive activity in FLT-3 ITD cells. In these cells, activity changes in singling molecules and apoptosis related molecules provided evidence for effective target modulation activities. We describe the implications of these findings with respect to the formulation of future clinical studies to treat children with high risk pediatric leukemia.

Keywords: Pediatric Leukemia, Pim-Inhibitor, FLT3

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