Abstract

VS-4718, a Potent FAK Kinase (FAK) Inhibitor, Exhibits Anticancer Activity in Leukemia Models in Vitro and in Vivo

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INTRODUCTION

The current chemotherapy for leukemia is effective in killing leukemic blasts in the peripheral blood, but not leukemic stem cells (LSCs) in the bone marrow, which is thought to be responsible for the high relapse rate in leukemia. Thus, new therapies that effectively target LSCs are urgently needed to prevent cancer relapse. Accumulating evidence supports an essential role for adhesion pathways particularly integrin beta 3 and its downstream target focal adhesion kinase (FAK) in the maintenance of LSCs.1,2 Previously, we have shown that FAK inhibitors preferentially target cancer stem cells in solid tumors.3,4 We are extending our investigation of FAK inhibitors into hematological malignancies and report here that the FAK inhibitor VS-4718 displays anticancer activity in leukemia models both in vitro and in vivo.

RESULTS

VS-4718 is a potent and orally bioavailable small molecule that targets cancer stem cells through inhibition of FAK which is currently being evaluated in a Phase 1 clinical trial (NCT01849744). The anti-proliferative effect of VS-4718 was evaluated in a panel of 10 cell lines derived from patients with acute myeloid leukemia (AML), T-cell acute lymphocytic leukemia (T-ALL), B-cell acute lymphocytic leukemia (B-ALL), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) using a CellTiter-Glo cell viability assay on tissue culture or collagen coated plates. VS-4718 displayed anti-proliferative effects against most of these cell lines, with MV4-11 AML being the most sensitive with an EC50 of 100 nM. We further investigated the in vivo efficacy of VS-4718 in both subcutaneous and disseminated xenograft models of AML using the MV4-11 cell line. Nude mice bearing subcutaneous MV4-11 tumors were treated orally twice daily (O.T.D.) with either vehicle control or VS-4718 for 14 days. The 75 mg/kg dosage of VS-4718 caused 50% tumor growth delay and significantly extended median survival of mice from 28 days to 48 days (p < 0.05). Moreover, tumor regression was observed in 4 out of 10 mice. We extended these observations to a disseminated MV4-11 AML model to incorporate bone marrow stromal biology. When compared with vehicle control, VS-4718 dosed at 25 or 75 mg/kg on an oral bid schedule for 14 days, resulted in a 40% and 76% increase in mouse life span, and significantly extended survival with p values < 0.005 and < 0.001 (log rank test), respectively. The effect of VS-4718 on leukemia stem cells and minimal residual disease (MRD) is currently under investigation.

CONFLICT OF INTEREST DISCLOSURE

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REFERENCES


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