Inhibition of acute leukemia by KYA1797K, Midostaurin: simultaneous downregulation of β-catenin and RAS

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* KYA1797K downregulated β-catenin and RAS together in leukemic cell lines and pediatric ALL samples.
* IC50 of KYA1797K was <5.0 µM in all leukemic cell lines regardless of RAS status.
* Midostaurin, small molecule inhibitor (SMI) for FLT3 mutation acting for multi-target, was less effective in FLT3 wild-type cell line.
* Relapse of leukemia originates from the subclones with leukemia-initiating cell (LIC). New treatment modalities is needed in addition to conventional chemotherapy to prevent relapse. SMI like KYA1797K could be a good candidate for LIC-oriented therapy.

Introduction

FLT3 mutation is highly related to poor prognosis and RAS mutation frequently occurs in subclones which have a high chance to relapse. Hyperactive RAS is also strongly associated with treatment resistance in leukemia. SMI therapy opened a new window for cancer treatment but targeting one subject have limited effect. Midostaurin not only inhibits FLT3 but also has multi-targets and is approved by FDA for AML recently (NEJM 2017). KYA1797K binds directly to RGS domain of Axin and stabilizes the β-catenin destruction complex which activates GSK3β and results in degradation of β-catenin and RAS.

Materials and methods

Leukemic cells (MOLT-4, Jurkat, KG-1, THP-1, U937, MV4;11, RS4;11) were cultured in RPMI1640 media under various concentration (0.1-10 µM for KYA1797k, 0.5-500 nM for Midostaurin) for 48h and with Erlotinib (1 µM) for comparison. Cell proliferation assay on each leukemic cell was done and Immunoblotting for β-catenin, GSK3β, Pan-RAS, N-RAS was checked. Downstream targets of Wnt pathway (c-Myc, CD44, LEF1, Met, TCF3/TCF7) were studied by Immunoblotting. MOLT-4 was stimulated with Wnt3a (200ng/mL, 4h) and changes in Wnt pathway was observed. BM samples of ALL patients were evaluated for β-catenin and RAS. Two of them with High-risk factor went through MACS for CD34+ selection and were treated with KYA1797K.

Results

A) Midostaurin
B) KYA1797K

We wish to start animal study with SMI such as KYA1797K and co-operate with other institutions to plan clinical trials. Since Wnt/β-catenin pathway and RAS-ERK pathway is frequently activated, we want to expand the research to solid tumors.