ABSTRACT

We previously found that activation of tyrosine kinase 2 (TYK2) contributes to the aberrant survival of T-cell acute lymphoblastic leukemia (T-ALL) cells (Sanda et al. Cancer Discov 2013), suggesting that molecular targeted strategies for TYK2 would be a promising strategy for treatment of T-ALL. In this study, we investigated therapeutic potential of novel TYK2 kinase inhibitor NDI-031301 in T-ALL. NDI-031301 treatment significantly reduced survival and selective inhibitory activity against TYK2 in a cellular context, because this compound specifically inhibited the growth of TYK2-activated Ba/F3 cells whereas Ba/F3 cells transformed by other tyrosine kinases showed decreased sensitivity. NDI-031301 induced growth inhibition and apoptosis in multiple human T-ALL cell lines. We found that treatment with 3 μM of NDI-031301 resulted in reduction of STAT1 Tyr701 phosphorylation and BCL2 levels in Ba/F3-TEL-K1 T-ALL cell line, consistent with our previous finding that TYK2 phosphorylates STAT1 and upregulates BCL2 expression in most T-ALL cells. Surprisingly, the treatment also uniquely led to activation of three mitogen-activated protein kinases (MAPKs), resulting in phosphorylation of ERK, SAPK/JNK and p38 MAPK coincident with PARP cleavage, which was not observed with the Jak-selective inhibitors tofacitinib and baricitinib. Activation of p38 MAPK occurred within 1 h of NDI-031301 treatment and was responsible for NDI-031301-induced T-ALL cell death, because pharmacologic inhibition of p38 MAPK by SB203580 partially rescued apoptosis induced by TYK2 inhibitor. Finally, daily oral administration of NDI-031301 at 190 mg/kg BID to immunodeficient mice engrafted with KOPT-K1 cells was well tolerated, and led to decreased tumor burden and a significant survival benefit. Thus, our findings clearly support TYK2 inhibition with NDI-031301 as a related compound as a potential therapeutic strategy for patients with T-ALL, and also raise the possibility that this approach may be clinically relevant, and may be an approach to accentuate its anti-leukemic activity.

OBJECTIVES

To analyze the antitumor potency of a novel TYK2 kinase inhibitor NDI-031301 against T-ALL and elucidate the mechanisms through which this compound induces apoptosis in the cells.

MATERIALS

- Cells
  - Ba/F3 cells transformed by each of constitutively active JAK family kinases (TEL-JAK1, TEL-JAK2, TEL-JAK3 and TEL-Y705K) or by an alternative tyrosine kinase, TEL-ABL
  - Human T-ALL cell lines: DU.528, KOPT-K1, HPB-ALL and SKW-3
- Reagents
  - NDI-031301 is a novel TYK2 kinase inhibitor from Nimbus Therapeutics. Tofacitinib and baricitinib are JAK kinase inhibitors under current clinical trials.

RESULTS

NDI-031301 is a potent and selective inhibitor of TYK2 tyrosine kinase

- NDI-031301 inhibits p38 MAPK
  - Activation of p38 MAPK is involved in NDI-031301-induced apoptosis

CONCLUSIONS

1. A novel TYK2 kinase inhibitor NDI-031301 induced cytotoxicity in human T-ALL cell lines tested, consistent with our previous result showing the growth and survival inhibition of these cells by TYK2 with shRNA. The anti-leukemic activity of NDI-031301 was recapitulated in a KOPT-K1 xenograft study, indicating that TYK2 inhibitor is able to efficiently suppress the growth of human T-ALL cells in vivo as well as in vitro.

2. TYK2 inhibition by NDI-031301 led not only to suppression of STAT1 phosphorylation, but also activation of MAPK signaling pathways in KOPT-K1 T-ALL cells.

3. Pharmacologic inhibition of p38 MAPK partially rescued apoptosis induced by NDI-031301, indicating involvement of the p38 MAPK pathway in TYK2-mediated survival of T-ALL cells.

Conflict of interest disclosure: C.E.M., W.M., J.R. and K.Y. are employees of Nimbus Therapeutics, and receive compensation and hold equity in the company. The remaining authors declare no conflict of interest.