Phosphorylated LCK as a response biomarker for Dasatinib sensitivity in T-ALL

Authors:
Jonne Nieminen, Charlotte Rinne, Laura Oksa, Merja Heinäniemi, Olli Lohi

Keywords:
Dasatinib, T-acute lymphoblastic leukemia, Drug sensitivity, LCK kinase, Phosphorylation

Abstract
T-cell acute lymphoblastic leukemia (T-ALL) arising from cortical thymocytes exploits pre–T cell receptor (pre-TCR) signaling to drive proliferation and survival. These survival signals depend on the kinase LCK, a central downstream component of the pre-TCR pathway. While *LCK* overexpression is common in T-ALL, it does not predict sensitivity to dasatinib. Instead, LCK activation is regulated by phosphorylation at multiple sites, with phosphorylation of tyrosine 394 (Y394) marking its active form. Dasatinib treatment abolishes Y394 phosphorylation, and early preclinical data suggest that pLCK(Y394) could serve as a biomarker for drug response.

Here, we investigated whether pLCK(Y394), assessed by flow cytometry, could provide a reliable and accessible biomarker for dasatinib sensitivity in T-ALL. We screened 11 T-ALL cell lines for pLCK(Y394) status: KOPTK1 cell line known for dasatinib hypersensitivity displayed high levels of Y394 phosphorylation, whereas Jurkat cells showed only modest levels. In contrast, J.CAM.1.6 cells—a Jurkat derivative with chemically induced deletion of *LCK*—showed no detectable phosphorylation, validating the assay. To assess drug sensitivity, we established a co-culture assay in which T-ALL cells are grown on hTERT-immortalized mesenchymal stem cells. Consistent with their Y394 phosphorylation status, Jurkat cells exhibited relatively poor sensitivity to dasatinib, the LCK-deficient J.CAM.1.6. cell line showed no response, while KOPTK1 cells were hypersensitive.

Next, we will expand these studies to approximately 50 primary T-ALL patient samples, aiming to correlate dasatinib sensitivity with LCK Y394 phosphorylation in an *ex vivo* setting. Ultimately, these data will be integrated into a European-wide initiative to evaluate the clinical feasibility of using pLCK as a response biomarker in the upcoming ALLTogether protocol.