Abstract

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive malignant hematological disorder arising in the thymus from T-cell progenitors. T-ALL mainly affects children and young adults, and remains fatal in 20% of adolescents and 25% of adults, despite progress in polychemotherapy protocols. Therefore, innovative-targeted therapies are needed for patients with poor prognosis. Aberrant activation of PI3K/Akt/mTOR signaling pathway is a common event in T-ALL patients and portends a poor prognosis. Recent findings have highlighted that constitutively active phosphatidylinositol 3-kinase PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway upregulates cell proliferation, survival, and drug resistance. These observations lend compelling weight to the application of PI3K/Akt/mTOR inhibitors in the therapy of T-ALL. Preclinical studies have highlighted that modulators of PI3K/Akt/mTOR signaling could have a therapeutic relevance in T-ALL. However, the best strategy for inhibiting this highly complex signal transduction pathway, is still unclear, as the pharmaceutical companies have disclosed an impressive array of small molecules targeting this signaling network at different levels. In this study we have analyzed the therapeutic potential of the novel dual PI3K/mTOR inhibitor NVP-BGT226, an orally bioavailable imidazoquinoline derivative, which has entered clinical trials for solid tumors and an ATP-competitive mTORC1/mTORC2 inhibitor Torin-2, on both T-ALL cell lines and normal T-lymphocytes samples. We found that NVP-BGT226 and Torin-2 displayed the most powerful cytotoxic effects against T-ALL cell lines and primary mitogenically stimulated T-lymphocytes while quiescent cells were not affected. NVP-BGT226 and Torin-2 treatment also resulted in cell cycle arrest, apoptosis, and autophagy. Western blots showed a dose- and time-dependent dephosphorylation of Akt and mTORC1 downstream targets in response to both drugs in T-ALL cell lines. Nevertheless, the effect of both drugs also was documented in mitogenic stimulated primary lymphocytes, while no effects there detectable in quiescent cells. We also documented that dual targeting of this pathway was significantly cytotoxic in T-ALL cells. This effect was absent in quiescent T-lymphocyte but present in mitogenically activated T-lymphocytes, at variance requiring a higher concentrations of drugs. This

observation indicates that vertical inhibition at different levels of the PI3K/Akt/mTOR network could be considered as a future innovative strategy for treating T-ALL patients.