Efficacy of phosphatidylinositol-3 kinase inhibitors with diverse isoform selectivity profiles for inhibiting the survival of chronic lymphocytic leukemia cells

Elisa Göckeritz, Susan Kerwien, Michael Baumann, Marion Wigger, Verena Vondey, Lars Neumann, Thomas Landwehr, Clemens M Wendtner, Christian Klein, Ningshu Liu, Michael Hallek, Lukas P Frenzel & Günter Krause

Pharmacological inhibition of phosphatidylinositol-3-kinase (PI3K)-mediated signaling holds great promise for treating chronic lymphocytic leukemia (CLL). Therefore we assessed three structurally related PI3K inhibitors targeting the PI3K-δ isoform for their ability to inhibit the survival of freshly isolated CLL cells. The purely PI3K-δ-selective inhibitor idelalisib was compared to copanlisib (BAY 80-6946) and duvelisib (IPI-145), with isoform target profiles that additionally include PI3K-α or PI3K-γ, respectively. The concentrations leading to half-maximal reduction of the survival of CLL cells were more than ten-fold lower for copanlisib than for idelalisib and duvelisib. At concentrations reflecting the biological availability of the different inhibitors, high levels of apoptotic response among CLL samples were attained more consistently with copanlisib than with idelalisib and duvelisib. Copanlisib selectively reduced the survival of CLL cells compared to T cells and to B cells from healthy donors. In addition copanlisib and duvelisib impaired the migration of CLL cells towards CXCL12 to a greater extent than equimolar idelalisib. Similarly copanlisib and duvelisib reduced the survival of CLL cells in co-cultures with the bone marrow stroma cell line HS-5 more strongly than idelalisib. Survival inhibition by copanlisib and idelalisib was enhanced by the monoclonal CD20 antibodies rituximab and obinutuzumab (GA101), while antibody-dependent cellular cytotoxicity mediated by alemtuzumab and peripheral blood mononuclear cells was not substantially impaired by both PI3K inhibitors for the CLL-derived JVM-3 cell line as target cells. Taken together, targeting the α- and δ- p110 isoforms with copanlisib may be a useful strategy for the treatment of CLL and warrants further clinical investigation.