

A reversible carnitine palmitoyltransferase I (CPT1) inhibitor offsets chronic lymphocytic leukemia cell proliferation

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Crucial for CLL development and progression are iterative cycles of cell re-activation and proliferation in lymphoid tissues. Since cellular fatty acid (FA) import and oxidation (FAO) were recently reported to be upregulated in CLL, we explored in-vitro effects of ST1326, a reversible inhibitor of carnitine-palmitoyl transferase 1A (CPT1A), on leukemic cells subject to activating microenvironment-mimicking stimuli.

ST1326 induced dose-dependent mitochondrial dysfunction and cell death, which were remarkably higher in activated/proliferating than quiescent CLL cells. Drug sensitivity was observed irrespective of the presence of *TP53* alterations or chromosomal abnormalities.

ST1326 cytotoxicity was associated with decreased levels of intracellular acetyl-CoA and phosphorylated STAT3, known to favor CLL cell proliferation and upregulate antiapoptotic Bcl-2 family members. Indeed, rising of Mcl-1 and Bcl-xl expression in response to microenvironment stimulation was impaired by ST1326. Drug combination experiments with the BH3-mimetic ABT-199/Venetoclax, whose effects are counteracted by Mcl-1/Bcl-xl and cell proliferation, showed strong ST1326-mediated potentiation of ABT-199 cytotoxicity in activated/proliferating CLL cells.

The data indicate that CLL cells turning to an activated/proliferating state become more dependent on FAO and more sensitive to FAO-antagonists, and pave the way for ST1326 as an adjuvant tool in anti-CLL drug-combination regimens with drugs that loose efficacy on proliferating leukemic cells.