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## Preclinical evaluation of sorafenib against B- and T-cell lymphoma



Intracellular signal transduction by kinase mediated phosphorylation is essential for survival and growth of lymphoma cells, and particularly in T cell lymphoma, high expression levels of PDGFR alpha have been observed. Aiming at a multikinase inhibition approach, we analyzed known sorafenib targets, and found at least two of raf family members, VEGFR2, PDGFR, c-kit or flt3 to be expressed in any of 11 cell lines representing major types of aggressive B- and T-cell lymphomas. After short time exposure sorafenib reduced cell viability at clinically relevant concentrations with IC<sub>50</sub> between 3.7 and 10.9 μM in most cell lines. Most sensitive were the diffuse large B cell lines SUDHL4 and Karpas422, as well as the Burkitt cell lines Ramos and Raji.

Induction of apoptotic death increased significantly with exposure time (24 through 72 h). In the remaining cells proliferative arrest occurred, leading to a complete loss of *in vitro* clonogenicity from all cell lines following 10 day exposure to sorafenib (7.3 μM), even after discontinuation of sorafenib exposure. Such cytostatic effects were also seen in 11 primary lymphoma cell samples, including 4 cases of T cell lymphoma. Sorafenib perturbed the activation of the RAF/MEK/ERK pathway, and induced the inhibition of AKT phosphorylation at degrees varying between cell lines. The concept of multikinase inhibition in PTCL will be clinically evaluated in the up-coming NEXavar in relapsed peripheral T-cell Non-Hodgkins lymphoma (NEXT) trial.