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Antitumor activity of new pyrazolo[3,4-d] pyrimidine SRC kinase inhibitors in Burkitt lymphoma cell lines and its enhancement by WEE1 inhibition.

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Source

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Abstract

Burkitt lymphoma (BL) is a highly aggressive B-cell neoplasm. Although intensive polychemotherapy regimens have proven very effective, they are associated with significant toxicities. Therefore, more rational therapies that selectively target the molecular abnormalities of BL are needed. Recent data suggest that the tyrosine kinase SRC could represent a therapeutic target for BL. We found that new pyrazolo[3,4-d]pyrimidine SRC inhibitors exerted a significant cytotoxic effect and induced apoptosis on two BL cell lines, as determined by MTS assays, cytofluorimetric analyses and caspase 3 assay. Notably, our SRC inhibitors proved to be more effective than the well-known SRC inhibitor PP 2 [4-amino-5-(4 chlorophenyl)-7-(dimethylethyl)pyrazolo[3,4-d]pyrimidine] in BL cells. Moreover, our small molecules induced a G2/M arrest in BL cells through a possible new mechanism, whereby SRC inhibition hinders an AKT-WEE 1-cyclin-dependent kinase 1 (CDK1) axis, leading to inhibition of CDK1, the main trigger of entry into mitosis. By using a small-molecule inhibitor of WEE 1, a crucial CDK1 negative regulator, we were able to shift the balance toward apoptosis rather than growth arrest and enhance the efficacy of the SRC inhibitors, suggesting a possible use of these selective drugs in combination for a safe and efficient treatment of BL.

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