ABSTRACT

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Title of diploma thesis:

THE POTENTIAL OF ALDO-KETO REDUCTASE 1C3 INHIBITION AS AN OFF-TARGET EFFECT OF ISOCITRATE DEHYDROGENASE 2 INHIBITOR ENASIDENIB IN LEUKEMIA

Acute myeloid leukemia (AML) involves an excessive proliferation of clonal myeloid blasts. Several drugs targeting AML mutations are under study, with enasidenib (ENA) as the first selective inhibitor of isocitrate dehydrogenases 2 (IDH2) mutants approved by the FDA. A current multicenter clinical trial has shown encouraging results of combining ENA with standard intensive induction therapy, including daunorubicin (Daun). However, expression in AML cells of ATP-binding cassette (ABC) transporters and the aldo-keto reductase family 1 member C3 (AKR1C3) may conduct extrusion and hydroxylation of Daun, respectively, that lessens Daun's cytotoxic effects. This study aimed to evaluate the effect of ENA on Daun accumulation and/or inactivation in the leukemic cell line KG1α. ENA produced a synergistic effect on Daun cytotoxicity in KG1α cells related to its higher accumulation and lower metabolization. Furthermore, AKR1C3 also catalyzes the conversion of prostaglandin D2 (PGD_2) to 9α and 11β-prostaglandin F2α (11β-PGF2α), which induces the proliferation of leukemic blasts. This work also provides a preliminary determination of ENA inhibiting AKR1C3 metabolization of PGD2 as well as KG1α cells proliferative induction by PGD2. In conclusion, this work deciphered novel IDH2-independent molecular targets for ENA that support its potential effectivity against AML without IDH2 mutations as well as its combination with standard chemotherapeutics like Daun in AML therapy.