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MEETING ABSTRACTS

ZANUBRUTINIB ACTS AS AN EFFECTIVE RESISTANCE MODULATOR BY INHIBITING ANTHRACYCLINE METABOLISM AND EFFLUX

Lucie Čermáková [1], Jakub Hofman [2], Vladimír Wsól [1]
Presenting author: Lucie Čermáková (cermakoval@faf.cuni.cz)

[1] Department of Biochemical Sciences, Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, 500 05 Hradec Králové, Charles University, The Czech Republic
[2] Department of Pharmacology and Toxicology, Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, 500 05 Hradec Králové, Charles University, The Czech Republic

Anthracycline (ANT) resistance represents a significant challenge in cancer therapy. Besides other mechanisms, ANT resistance is mediated by the metabolic activity of carbonyl-reducing enzymes (CREs) and/or the efflux activity of ATP-binding cassette (ABC) transporters. CREs reduce ANTs to their corresponding less potent alcohol metabolites, while ABC transporters pump ANT drugs out of cancer cells decreasing their concentrations below cytotoxic level. Among CREs, AKR1C3 is of great importance because its overexpression has been detected in many hematological and solid malignancies, similar to some ABC transporters such as ABCB1, ABCG2, and ABCC1. In the present study, we describe the effect of Bruton´s tyrosine kinase inhibitor, zanubrutinib (ZAN), on ANT carbonyl reduction catalyzed by AKR1C3 and ANT active efflux mediated by ABC transporters. Our results show potent inhibition of recombinant AKR1C3, while the interaction was confirmed at the level of intact cells as well. Subsequent experiments proved a synergistic effect of combination of ZAN with daunorubicin in cancer cells with AKR1C3 overexpression. In gene induction studies, ZAN did not affect the mRNA level of AKR1C3. Finally, using ANT accumulation assays, ZAN was found to significantly inhibit ABC transporters ABCB1 and ABCC1, suggesting additional mechanism contributing to combatting ANT resistance. In summary, our data introduce ZAN as an effective modulator targeting multiple pharmacokinetic resistance mediators. Following *in vivo* confirmation, our data might be translated into the therapy of ANT resistant tumors.

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Keywords: multidrug resistance; AKR1C3; ABC transporter; zanubrutinib