ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Biochemical Sciences
Candidate: Bc. Lucie Čermáková
Supervisor: RNDr. Eva Novotná, Ph.D.
Title of diploma thesis: The effect of acalabrutinib and ibrutinib on the efficacy of daunorubicin in cancer cells

Leukemia presents malignant diseases of hematopoiesis, which essence is the malignant transformation of a hematopoietic stem cell at various levels of maturation and increased proliferative activity. Chemotherapy is the gold standard in the treatment of leukemia. One of the many treatments is the use of anthracycline chemotherapeutics, especially daunorubicin (DAU). Anthracyclines are widely used in clinical practice but have high cardiotoxic effects that limit their dosage. One of the main causes of side effects is the reduction of an anthracycline chemotherapeutic to the appropriate toxic metabolite, which accumulates in the heart. Carbonyl, reducing enzymes from the superfamily aldo-ketoreductase (AKR), and short-chain dehydrogenase/reductase (SDR) are involved in this reduction. At the same time, carbonyl reducing enzymes, has been shown to be involved in the mechanisms that cause tumor cells to be resistant to anthracyclines, thereby reducing the inhibition of the growth of these cells.

In the diploma thesis we found that selected tyrosine kinase inhibitors (acalabrutinib, ibrutinib) inhibit the activity of the enzyme AKR1C3 at the cellular level. To determine the inhibitory effect, we selected the HCT116 cell line transiently transfected with a plasmid encoding the AKR1C3 enzyme. The results demonstrated the ability of acalabrutinib and ibrutinib to inhibit AKR1C3 and thus reduce DAU to daunorubicinol. We further determined the effect of the combination of DAU with acalabrutinib and ibrutinib on the KG1α cell line with natural AKR1C3 expression. The results show that the combination of DAU with ibrutinib reduces the viability of KG1α more than DAU or ibrutinib alone. This suggests that the ability of ibrutinib to inhibit DAU reduction can be used to increase the therapeutic effect of DAU while reducing the incidence of DAU side effects. We did not show a significant effect on the viability of the KG1α cell line with acalabrutinib.