Abstract

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Title of diploma thesis: The influence of midostaurin, vistusertib and talazoparib inhibition on the activity of selected reductases from AKR and SDR superfamilies.

Key words: reductase, AKR, inhibitors, midostaurin, vistusertib, talazoparib, anthracyclines, KG1a

Multi drug resistance is for a lot of years still a big problem in therapy of cancer. Anthracycline antibiotics are highly efficient for treating cancers but multi drug resistance and severe side effects sometimes restrain the use of them and lead therapy to fail. One of the worst adverse effect is a cardiotoxicity. By older studies, the mechanism of a cardiotoxicity was because of formation of reactive oxygen species (ROS). Many times, the negative effects of ROS on cardiac muscle cells was confirmed but nowadays the evidence opens some other and more complex mechanisms of its damage.

The main point of this work was examination of enzymes which metabolize anthracyclines, mainly daunorubicin. Metabolites which are formed are less potent than parent drug and they have bigger toxicity. This can have an impact on therapy and can cause a cardiotoxicity.

In our study we used 3 inhibitors, midostaurin, vistusertib, talazoparib and we tested their inhibition potential on daunorubicin reducing enzymes AKR1A1, AKR1B10, AKR1C3, AKR7A2 and CBR1. On the base of our results, the most inhibited enzyme is AKR1C3, which is valid for all 3 inhibitors tested. Most efficient inhibitor for AKR1C3 is midostaurin (93 % of inhibition with 50 μM). Inhibition of AKR1B10 is most efficient with vistusertib (38 % of inhibition with 50 μM). Others inhibit the enzyme only up to 18 % with 50 μM. We have similar results with AKR1A1, for which the most efficient inhibitor is midostaurin (28 % of inhibition with 50 μM). The weakest inhibition is shown

in AKR7A2 with maximal inhibition of 27 % with 50 μM of vistusertib. Other inhibitors show no efficiency against AKR7A2. We have not found a significantly potent inhibitor for CBR1. The highest inhibition of CBR1 was found for vistusertib (52 % of inhibition with 50 μM).

We finished this work by doing inhibition tests on cell line KG1a with midostaurin. By this test we confirmed higher cytotoxic effect of daunorubicin in presence with midostaurin.