Abstract

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Title of diploma thesis: Antiproliferative activity of novel dexrazoxane analogues and their effect on antitumor effectiveness of anthracyclines

Athracycline antibiotics (such as daunorubicin, doxorubicin or epirubicin) belong to the most common terapeutics of both solid tumors and hematological malignities. Unfortunately the serious and life-threatening adverse effect cardiotoxicity compromises their clinical usefulness. The only approved protection against anthracycline cardiotoxicity so far is dexrazoxane. Despite the outstanding cardioprotective ability, dexrazoxane use is very limited mainly due to its possible side effects. So we were directed towards synthesis of dexrazoxane analogues with better pharmacological properties.

The aim of this diploma thesis was to assess the antiproliferative activity of novel analogues of both dexrazoxane (MK-15 and ES-5) and ADR-925 (JR-159 and KH-TA4) and their influence on the antiproliferative effectiveness of anthracyclines. Moreover, we aimed to study their chelating properties and their inhibition of the topoisomerase II in solution.

We tested the antiproliferative activity of the novel analogues using the promyelotic leukemia HL-60 cell line. Cellular viability was assessed with MTT test after 72 hours of incubation of cells with novel analogues alone or in combination with daunorubicin on 96-well plates at a density of 10,000 cells per well. Iron displacement from its complex with anthracyclines was measured spectrophotometrically by the changes of the daunorubicin-Fe complex specific absorbation at 600 nm over time.The results show statistically significant drop in the HL-60 proliferation caused by dexrazoxane and KH-TA4. The novel agents (10 and 100 μM) did not compromise the antiproliferative action of 15 nM daunorubicin (IC_{50} value). From the novel analogues, only JR-159 was able to at least partially displace iron from its daunorubicin complex. The relaxation activity of topoisomerase II was inhibited by 100 μM dexrazoxane.