Abstract

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Title of Doctoral Thesis:

Cardiotoxicity of antineoplastic drugs: Study of the molecular mechanisms and the possibilities of pharmacological cardioprotection.

Anthracyclines are amongst the most widely used antineoplastic agents. Nevertheless, their use is limited by the risk of cardiotoxicity. Dexrazoxane has been the only approved cardioprotectant against anthracycline cardiotoxicity so far. Despite half a century of research, the mechanisms of its cardioprotective ability as well as the mechanisms of anthracycline toxicity are elusive. In this study, we focused on the study of the molecular mechanisms of dexrazoxane cardioprotection. We did not prove the principal role of glutathione and related antioxidant enzymes in the pathogenesis of anthracycline cardiotoxicity both in the *in vitro* experiments and *in vivo* in the samples of left ventricles from the well-established model of chronic anthracycline cardiotoxicity in rabbits. Moreover, we found that *in vitro* dexrazoxane is able to protect the isolated neonatal rat cardiomyocytes against anthracycline-, but not hydrogen peroxide-induced damage. As dexrazoxane is also a catalytic inhibitor of topoisomerase II, we compared its cardioprotective ability with two other topoisomerase II catalytic inhibitors, sobuzoxane and merbarone. All dexrazoxane, sobuzoxane and merbarone were comparably effective in the protection of neonatal rat cardiomyocytes against anthracycline toxicity, but were uneffective against oxidative damage. At the same time, the catalytic inhibitors used in this

study did not compromise the antiproliferative activity of antrhracyclines on the HL-60 cell line. The structure-activity relationships of the dexrazoxane cardioprotection are not precisely determined, as well as the need of its hydrolysis to the metal-chelating metabolite ADR-925. Therefore, we studied the newly synthesized analogues of both dexrazoxane and ADR-925 regarding their cardioprotective potential. We found that these novel analogues are not protective compared to dexrazoxane, which is probably caused by their inactivity regarding topoisomerase II catalytic inhibition. From the data of this study as well as from the experimental data of other recent studies we can conclude, that rather than by the traditionally proposed oxidative damage, anthracyclines may be cardiotoxic due to their interaction with the topoisomerase II in cardiomyocytes.