SUMMARY - CARDIOTOXICITY OF ANTHRACYCLINE ANTINEOPLASTIC DRUGS AND POSSIBILITIES OF PHARMACOLOGICAL CARDIOPROTECTION

Chronic anthracycline (ANT) cardiotoxicity is an important clinical problem which can have a substantial impact on morbidity and mortality of cancer survivors. Dexrazoxane (DEX) is the only agent with clearly evidenced cardioprotective effects in both experimental models and clinical trials. Despite intensive research, precise pathogenesis of chronic ANT cardiotoxicity and molecular mechanisms of cardioprotective effects of DEX remain unknown. Current clinical guidelines recommend not using DEX from the beginning of ANT therapy, but instead only from the cumulative ANT dose of 300 mg /m2.

The aim of this work was to study functional, morphological and molecular changes associated with induction of chronic ANT cardiotoxicity and their further development in the post-exposure (follow up) period. Special attention was paid on the role of oxidative stress and possible response of protective antioxidant pathway regulated by Nrf2 as well as on mitochondrial impairment and response of mitochondrial biogenesis pathway. Chronic ANT cardiotoxicity was induced in rabbits by repeated intravenous injections of daunorubicin (DAU, 3 mg/kg, once weekly for 10 weeks). At the end of the treatment, the animals were randomized for sacrifice or for 10 week post-exposure follow up. DAU administration induced significant systolic dysfunction already at the end of treatment, while further progression into congestive heart failure and left ventricle dilation was observed in the follow up period. Cardiac troponin T plasma raise persisted several weeks after the end of DAU exposure which suggests continuing cardiomyocyte damage even in the post-exposure period. Although signs of oxidative insults were detected in the myocardium, their limited or absent association with left ventricle dysfunction is not suggesting the direct and executive role of oxidative damage in the pathogenesis of chronic ANT cardiotoxicity. Repeated dosing with DAU also did not activate cytoprotective and antioxidant Nrf2 pathway and available data do not imply its significant role in this toxicity. DAU administration induced significant damage to mitochondrial functions. However, this was not associated with the activation of mitochondrial biogenesis pathway. On contrary, the pathway seemed to be suppressed, particularly in the post-exposure follow up. This may explain the progression of the cardiac damage in this period.

Another aim of this thesis was to use the above described experimental model to compare the cardioprotective effects of DEX when administered from the very first ANT dose (early cardioprotective intervention) compared to the administration following current guidelines (delayed cardioprotective intervention). DEX (60 mg/kg) was administered before each DAU dose or commencing the 7^{th} DAU administration (cumulative DAU dose of 300 mg/m^2). Both schedules prevented occurrence of premature deaths and severe congestive heart failure, but they were substantially different each other in the efficacy. Most of evaluated parameters clearly indicated that the early cardioprotective intervention achieved markedly better outcomes. In this group no changes were found in the systolic and diastolic function in both treatment and follow up period, cardiac morphology was comparable as in the controls group and no changes were observed in plasma concentrations of cardiac troponin T. This contrasted with delayed cardioprotective intervention where DEX administration only prevented further progression of the subclinical cardiac damage towards heart failure. Obtained data also did not indicate that the cardioprotective effects are directly dependent and proportional to changes in oxidative stress parameters. Early DEX administration also effectively prevented the onset of mitochondrial damage and impairment of the expression of respiratory chain subunits encoded by both mitochondrial and nuclear genome; however, this protection was not based on the common mtDNA deletions prevention.

The results of this thesis provide novel insights into the mechanisms of chronic ANT cardiotoxicity and contribute to the discussion about the optimal schedule of DEX administration. Cardioprotective effects of DEX obviously deserve further study since the mechanism of cardioprotection may hold the key to the mechanisms of ANT cardiotoxicity. Moreover, it could contribute to the development of novel effective strategies for protection of the heart from this toxicity.