Mitochondrial dysfunction associated with AC mode of chemotherapy intake

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Funding Acknowledgement: Type of funding source: None

Since the establishment of the anthracycline drugs cardiotoxigenic effect, the most widely accepted mechanistic base for their iatrogenic cardiotoxicity was connected with excessive and inadequate intensification of LPO. However, ineffectiveness of the antioxidant and multivitamin regimens of cardio-protection caused the necessity of finding new pathogenic targets, exposure to which will prevent the development of cardiovascular symptoms. Such a target became the nuclear topoisomerases, the study results of which served as the foundation for the creation of dexrazoxan, the only drug with this regard approved by the FDA. However, our interest was attracted towards the mitochondrial topoisomerases, since the integrity of the mitochondrial apparatus of cardiomyocytes is the basic link in maintaining the physiological morpho-functional balance of cardiomyocytes. At the same time, it is established that in the cell doxorubicin is predominantly accumulated in the mitochondria, which also makes emphasizes onto the prospects of studying this issue.

Purpose: Purpose of the study was to investigate the influence of AC mode of chemotherapy (adriamicin (doxorubicin) + cyclophosphomide) on the mitochondrial topoisomerases levels.

Methods: 60 inbred mice of the C57BL/6J line with genotype a,H-2b were used. The experimental animals were divided into 2 groups: in the first group polychemotherapy in AC mode was applied; in the second group (placebo group) saline solution was used. Doxorubicin (Sigma Aldrich) was administered at a dose of 4 mg/kg and cyclophosphamid (Sigma Aldrich) at a dose of 2 mg/kg were administered intravenously. There were 4 courses conducted with the intervals of 21 days between them. The study results were recorded in 6 days after the last cycle of chemotherapy. The total duration of experiment was 90 days. The following types of topoisomerases have been studied: Top2β, Top3α, and Top1mt.

Results: The results of the first group showed a decrease in the Top2β level by 2.4±0.4%, Top3α - by 0.7±0.5, and Top1mt - by 49.5±11.7% (p=0.05). When analyzing the results of the second group no statistically significant changes were recorded.

Conclusion: The fact of AC mode of chemotherapy administered should be taken as a predictor of destabilization of the mitochondrial topoisomerases signaling, in particular of the Top1mt, which in turn, causes the development of mitochondrial dysfunction and results the energy imbalance in cardiomyocytes.