Abstract

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Cancer is a serious societal health problem, which can affect each of us, and its incidence increases rapidly with age. Anthracycline antibiotics (ANT) are extremely effective drugs that have been used to treat a number of cancers. They have a multimodal mechanism of action, one of them being the inhibition of topoisomerase 2 (TOP2), an essential cellular enzyme modulating DNA topology. Currently, use of ANTs is limited due to concerns about the occurrence of cardiotoxicity.

Etoposide (ETO) is an antitumor agent that acts as topoisomerase poison. ETO is often used in combination therapy with ANTs, but it is not considered significantly cardiotoxic. Dexrazoxane (DEX) is the only approved cardioprotectant against cardiotoxicity of ANTs. However, it does not act as chelating agent, as previously thought, but through inhibition of TOP2. Although DEX has been shown to be a very potent cardioprotectant, it also has its disadvantages. DEX has been associated with the occurrence of secondary malignancies.

The aim of the study was to determine whether other inhibitors of TOP2, namely (BNS-22, XK-469, ICRF-193) affect antiproliferative effect of ETO on the HL-60 leukemic cell line. For the tested agents, concentrations corresponding with their IC_{50} were determined and on the basis of this concentration their antiproliferative effects were evaluated both alone and in combination with ETO. For determination of cell viability, MTT assay was used. According to our results none of the tested substances significantly reduced the antitumor effect of ETO on HL-60 cells. On the contrary, ICRF-187 and ICRF-193 in combination with ETO showed a synergistic effect. BNS-22 and XK-469 also showed synergistic effect, but only in concentration around the IC_{50}, in other concentrations they seemed to be rather antagonistic.