Investigation of antiproliferative activity and mechanisms of action of quinoline derivatives for potential application in cancer therapy

SUMMARY

Due to the high incidence of cancer and the associated high mortality rate, the search for new drugs and effective therapies is extremely important. Understanding the molecular mechanisms of action of potential anticancer agents and continuously improving their properties is a very significant goal for modern science. An additional major problem related to drug resistance of cancer cells are numerous mutations, which rapidly change the conformations of molecular targets for anticancer drugs. Therefore, it is essential to design and synthesis of new compounds with multidirectional antiproliferative properties against cancer cells. In the realization of this goal, privileged structures, which are usually low molecular weight heterocyclic compounds, are often used. Among them, quinoline is particularly noteworthy as it is characterised by a wide spectrum of biological properties. The diversity of biological activity of compounds based on quinoline scaffold depends on the distribution of substituents.

New styrylquinoline and furanylvinylquinoline derivatives were analysed in this work. Their antiproliferative activity was evaluated *in vitro* on a panel of human cancer cell lines of different origin and p53 protein status. Among the analysed compounds, those with the best therapeutic properties were selected. For them, the potential mechanism of action was determined with particular emphasis on the induction of oxidative stress. Using a microcapillary flow cytometry technique, the effect of tested derivatives on cell cycle progression and the type of cell death induced by them were studied. Moreover, a time-dependent increase of intracellular reactive oxygen species (ROS) and changes in the level of one of the main cellular antioxidants, glutathione, were presented. Potential mechanisms of action were also confirmed at the mRNA and protein levels by analysing changes in the expression of specific molecular targets related to oxidative stress, the cell cycle and apoptosis.

The obtained results showed that a significant role in improving the activity of the tested derivatives was played, among others, by the addition of a hydroxyl group at the C8 position and the halogenation of the quinoline ring by chlorine atoms. Substitution of the nitro group in the styryl or furanylvinyl substituent also enhanced the anticancer activity. The tested compounds also caused inhibition of cell cycle in S or G2/M phase and induced cell death through apoptotic pathway. During incubation with all selected derivatives, disturbances in the oxidoreductive balance of cells were also observed as a result of the ROS generation with concomitant changes in glutathione levels, ultimately leading to its significant decrease. Furthermore, the mechanism of styrylquinoline derivatives was shown to be hypoxia-induced and p53-independent. In contrast, tested furanylvinylquinoline analogue activated the p53, whereas the hypoxia-inducible factor did not. Furthermore, differences in the expression levels of selected genes and proteins also indicated a significant effect of p53 status in the mechanism of action of this compound.