TOPOISOMERASE INHIBITORS AND MULTIDRUGS RESISTANCE

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Introduction. The nuclear enzymes topoisomerase inhibitors I and II are critical for DNA function and cell survival and recent studies have identified these enzymes as cellular targets for several clinically active anticancer drugs. Topoisomerase II inhibitors (anthracyclines, epipodophyllotoxins, etc.) are active against several types of tumors. However, treatment with these drugs often results in the development of the multi-drug resistance. Because topoisomerase II-active drugs have several different modes of action, different mechanisms of resistance, including decreased activation and increased detoxification by glutathione-dependent enzymes, have also been implicated.

Aim. The aim of the study was to study the biochemical mechanisms of action of topoisomerase inhibitors and the possibility of drug resistance in the case of their use.

Materials and methods. In order to achieve this goal, an information search was conducted in the materials of scientific articles.

Results and discussion. Topoisomerase II is a target of alkaloid, anthracycline and related antitumor agents. Two types of multiple drug resistance are associated with these enzymes. In classical (typical) multidrug resistance, inhibitors are actively effluxed from cells by P-glycoprotein. In atypical multidrug resistance, topoisomerase II is either reduced in cellular content or mutated to a form that does not interact with inhibitors. Because cytotoxicity of most antineoplastic topoisomerase II inhibitors is directly related to the number of active topoisomerase II molecules, a reduction in this number leads to resistance. In the topoisomerase II mechanism, through which the DNA linking number is altered, DNA double strands are cleaved, and the termini transiently bound covalently (5′) or noncovalently (3′) to the enzyme while a second double strand is passed through the break in the first.

Conclusions. Multidrug resistance results from either 1) decreasing cellular content of the inhibitor by P-glycoprotein (typical) or 2) decreasing cellular content and/or activity of the target, topoisomerase II, as, for example, when its content or activity is modulated downward by decreased expression, deactivation, or by mutations to the topoisomerase II gene, producing an enzyme that reacts poorly with inhibitors (atypical). Mixed types, both typical and atypical, are known. Attempts to abrogate or prevent both typical and atypical multidrug resistance to topoisomerase II inhibitors have been described.

IMMUNOMODULATING PROPERTIES OF VITAMIN D AND DIABETES TYPE 1

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Introduction. Vitamin D (VD) is traditionally classified as a fat-soluble vitamin, while its derivative calcitriol belongs to hormones. Indeed, calciferol is an important nutrient that, after