THERAPEUTIC POTENTIAL OF ARSENIC TRIOXIDE (ATO) IN TREATMENT OF HEPATOCELLULAR CARCINOMA: ROLE OF OXIDATIVE STRESS IN ATO-INDUCED APOPTOSIS

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Abstract: Hepatocellular carcinoma (HCC), the dominant form of primary liver cancer, is the sixth most common cancer in the world with more than 700,000 people diagnosed annually. Arsenic trioxide (ATO) has been shown to be a potent anticancer agent in various carcinomas, proving particularly effective in the clinical treatment of relapsed and refractory acute promyelocytic leukemia. However, its bioactivity and molecular mechanisms against HCC has not been fully studied. Using human HCC (HepG²) cells as a test model, we studied the effects of ATO and examined the role of oxidative stress (OS) and apoptosis in cytotoxicity. OS biomarkers showed a significant increase (p< 0.05) of malondialdehyde concentrations, and a gradual decrease of antioxidant enzymes (GPx & CAT) activities with increasing ATO doses. Flow cytometry data showed a dose dependent increase in annexin V positive cells and caspase 3 activities. These results were confirmed by data of the DNA laddering assay showing a clear evidence of nucleosomal DNA fragmentation, as well as data from Western blotting showing a significant modulation of specific apoptotic related proteins, including the activation of p53 and p21 expression and the downregulation of Bcl-2 expression in ATO-treated cells. Taken together, our research demonstrates that ATO has a potential therapeutic effect against HCC, and its cytotoxicity may be mediated via oxidative stress and activation of the mitochondrial or intrinsic pathway of apoptosis.

Keywords: ATO: Arsenic Trioxide; MTT: 3-(4,5-Dimethyl-2-Thiazolyl)-2,5-Diphenyl-2tetrazoliumbromide; MDA: Malondialdehyde; CAT: Catalase; Gpx: Glutathione Peroxidase; PI: Propidium Iodine; Bcl-2; p21; p53

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