POTENTIAL THERAPEUTIC EFFECTS OF VITAMIN D₃ AND ARSENIC TRIOXIDE ON HUMAN LEUKEMIA (HL-60) CELLS

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Abstract: Arsenic trioxide (ATO) is a novel form of therapy that has been found to aid acute promyelocytic leukemia (APL) patients. Our laboratory has demonstrated that ATO stimulates oxidative stress therefore causing ATO-induced cytotoxicity in human leukemia (HL-60) cells. Pro-oxidants have been known to play a role in free radical-mediated oxidative stress. Cholecalciferol (vitamin D₃), an active metabolite of vitamin D, inhibits the growth of a number of cancer types such as prostate, breast, colorectal, leukemia, and skin cancers. The central goal of the present research was to use human leukemia (HL-60) APL-cells as an in vitro test model to evaluate whether low doses of vitamin D₃ potentiates the toxicity of ATO is mediated via apoptotic pathways. HL-60 cells were treated either with a pharmacologic dose of ATO alone and with several low doses of vitamin D₃. Cell survival was determined by MTT assay. Cell apoptosis was measured both by flow cytometry (Annexin-V) assessment, and DNA laddering assay. MTT assay indicated that vitamin D₃ co-treatment potentiates the ATO toxicity in HL-60 cells in a dose dependent manner. A statistically significant and dose-dependent increase (p <0.05) was recorded in annexin V positive cells (apoptotic cells) with increasing doses of vitamin D₃ in ATO-treated cells. This finding was confirmed by the result of DNA ladderling assay showing clear evidence of nucleosomal DNA fragmentation in vitamin and ATO co-treated -HL-60 cells. The present study indicates that vitamin D₃ potentiates the antitumor effects of ATO is mediated at least part, through phosphatidylinerse externalization and occurrence of nucleosomal DNA fragmentation. These findings highlight the potential impact of vitamin D₃ in promoting the pharmacological effect of ATO, suggesting a possible future role of vitamin D₃/ATO combination therapy in patients with acute promyelocytic leukemia (APL).

Keywords: Cholecalciferol (Vitamin D₃), arsenic trioxide, HL-60 cells, oxidative stress, apoptosis

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