ASCORBIC ACID AND ARSENIC TRIOXIDE AS POTENT MODULATORS OF OXIDATIVE STRESS AND MORPHOLOGICAL CHANGES CHARACTERISTICS OF APOPTOSIS IN HUMAN LEUKEMIA (HL-60) CELLS

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Abstract: Apoptosis (programmed cell death) has emerged as an important biologic mechanism that contributes to the maintenance of the integrity of multicellular organisms. Impairment of apoptosis has been implicated in many human diseases including cancers. Arsenic trioxide (ATO) has been recommended for the treatment of refractory cases of acute promyelocytic leukemia (APL). Recent studies in our laboratory indicated that oxidative stress plays a key role in ATO-induced cytotoxicity in human leukemia (HL-60) cells. In the present investigation, the lipid peroxidation assay was performed to determine the levels of malondialdehyde (MDA) production in HL-60 cells co-exposed to ascorbic acid (AA) and ATO, and to elucidate whether AA modulates oxidative stress induced by ATO in these cell lines. Apoptosis was assessed by cell morphology using a confocal microscope and images were obtained using a digital camera. Data obtained from the lipid peroxidation assay demonstrated that the addition of AA to ATO-treated HL-60 cells significantly increase (p <0.05) the production of MDA, an end product of lipid peroxidation compared to ATO alone. By using the confocal microscopy, we found that ATO induced apoptotic morphology in HL-60 cells compared to the control. Moreover, co-administration of AA plus ATO significantly induced cell death compared to ATO alone. The current study clearly demonstrates that AA potentiates ATO-induced oxidative stress in HL-60 cells, leading to growth arrest and apoptosis. Based on these direct in vitro findings, our studies provide evidence that AA may extend the therapeutic spectrum of ATO for the treatment of acute promyelocytic leukemia and other malignancies resistance to ATO.

Keywords: Arsenic trioxide, HL-60 cells, MDA, ascorbic acid, cell morphology

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