Arsenic Trioxide, an Old Drug? or a New Drug?

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The medicinal use of arsenic and its derivatives dates back more than 2000 years around the world. Arsenic was viewed as both a therapeutic agent for several diseases including cancer and also as a poison (1). Recently, arsenic has received renewed attention since the successful clinical application of arsenic trioxide (As$_2$O$_3$, ATO) for treating acute promyelocytic leukemia (APL) (2–4). ATO has been shown to induce the differentiation and apoptosis of APL cells both in vitro and in vivo in animal models (5). ATO is also a potent inducer of apoptosis in a number of cell types other than APL including acute myeloid leukemia (AML), gastric cancer, neuroblastoma, MC-CAR myeloma cells, malignant glioma, prostate cancer, gynecological cancers, and esophageal carcinoma (6–12).

The exact mechanism of ATO-induced apoptosis is unclear. ATO might induce apoptosis possibly by indirectly impairing H2O2 catalysis with resulting mitochondrial damage, histone deacetylase activation, blocking of cells in the G1 phase by inducing p21 in MC-CAR myeloma cells (8,13,14). ATO might additionally affect tumor cell growth by inhibiting angiogenesis (15).

ATO acts on cells through a variety of mechanisms, influencing numerous signal transduction pathways (16). Because of the many pathways involved in mediating the effects of arsenic, there is the potential for synergism with other agents to provide an enhanced therapeutic benefit. IL-1$\beta$ and IL-6, IFN, ascorbic acid, and retinoic acid and were implicated as agents with synergistic effects with ATO (17–19). In addition to the above list, we have shown that there is some synergy with ATO and ionizing radiation (20). It has also been demonstrated that ATO synergistically induces apoptosis via the up-regulation of the death receptor such as Fas and the TRAIL receptor (21,22). This paper also suggest that ATO might enhance the level of TRAIL-induced apoptosis and overcome the TRAIL resistance in multiple myeloma cells (23). Such combinations may result in the enhanced antitumor activity with acceptable tolerability. However, their rational development will require significant additional effort to understand the many molecular actions of arsenic in cells.

We might call arsenic an old drug, as a resurrection of an ancient drug from the list of carcinogens through modern science and technology. However, arsenic is a new weapon against cancer with a small molecular weight, various working mechanisms, and most importantly, no myelosuppression. In addition to ATO, Tetra-arsenic tetra-sulfide (As$_4$S$_4$) has also demonstrated some efficacy against APL (24). In addition to the above arsenicals, we reported that Tetraarsenic oxide (As$_2$O$_4$, TetraAs$^+$) is effective in inducing apoptosis against As$_2$O$_3$ resistant U937 leukemia cells and exhibits strong in vitro and in vivo antiangiogenic effects (25,26). More arsenic compounds might be expected to be developed and will be tested for their potential as anticancer agents. However, despite the above observations, more work will be needed in order to clarify the mechanism(s) responsible for the arsenic-mediated anticancer effects, and to fully assess its clinical potential.

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