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Review

Arsenic Trioxide; a Novel Therapeutic Agent for Prostate and Bladder Cancers

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HIGHLIGHTS

- Arsenic trioxide is a toxin with potential antitumor activity.
- Cell signaling pathways like PI3K/AKT and VEGFA-VEGFR2-PI3K/ERK can be the target of ATO.
- ATO in combination with inhibiting glutathione synthesis cantreat bladder cancer.

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ABSTRACT

The effectiveness of Arsenic Trioxide (ATO) in treating blood diseases is one of the most striking developments in modern medicine. One of the most important benefits of ATO is the failure of bone marrow suppression. ATO has been proposed as a novel and effective medicine for cancer prevention and treatment with various functions including, induction of apoptosis through re-activating the Wnt inhibitor, growth inhibition via activation of phosphatidylinositol 3-kinase (PI3K)/AKT pathway, autophagy stimulation, induction of cell differentiation and angiogenesis via vascular endothelial growth factor A (VEGFA)-VEGFR2-PI3K/ extracellular signal-regulated kinase (ERK) signaling path in cancer cells and ATO may be involved in the acetylation of histones and interfering with gene transcription. ATO can increase the synergistic effect in treatment and increased antitumor effects on prostate cancer cells via inhibiting Akt/mTOR signaling pathways, and so, ATO in combination with inhibiting glutathione synthesis can treat bladder cancer epithelial cells effectively.

Keywords: Arsenic Trioxide; Cancer Cells; Angiogenesis; Apoptosis

Introduction

Today, despite advances in the introduction of new drugs, treatment with anticancer drugs including cytotoxic drugs such as arsenic trioxide is still promising. Arsenic trioxide with the chemical formula As2O3 is a chemical compound. Its molar mass is 197.841 g/mol, Density 3.74 g/cm3, melting point of 312.2°C (594°F, 585.3° Kelvin), Boiling point 465 °C, 738K, 869 °F, Solubility in water 20 g/L (25 °C). The appearance of this compound is white solid. There is ample evidence that Arsenic Trioxide (ATO) has the anticancer potential against various types of human malignancies. Nowadays, the efficacy of ATO in the treatment of blood diseases is one of the most

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exciting developments in modern medicine (1). Although known as ATO as a toxin, it is also known as an ancient drug in the world and has been used for years to treat infections and cancer. In the past, ATO has been used in traditional Chinese medicine to treat psoriasis, syphilis, and rheumatism (2). In ancient Greece and Rome, ATO was used as a medicine and as a poison (3). Until the detection of penicillin in traditional western medication, it was used to treat syphilis, and successively, they were approved only for the treatment of central nervous system trypanosomiasis due to the oncogenic effects (4). In 1995, The Food and Drug Administration issued the ATO (As2O3) license (5). Liver toxicity has been informed as one of the major complications of this drug in patients (6, 7). One of the advantages of ATO over other cytotoxic drugs in the treatment of cancers is the failure of bone marrow suppression. Research on ATO and ongoing clinical trials are drawing a very good future for ATO in the treatment of malignant diseases. ATO is present in the soil, air, and in three metallic, trivalent, and pentavalent forms, which in the past have been used as Spirocheticidal Trypanocidal, which is more toxic than other forms due to eye complications. Trivalent and pentagonal forms of ATO have high digestive uptake. Of its three mineral forms, ATO is expressed as white ATO. On the other hand, the mechanism of ATO cell death is still unclear, whether in blood cancers or solid cancers. ATO is an effective antitumor drug for inhibiting the growth and proliferation of different types of tumor cells by various mechanisms. The anticancer effects of ATO on a wide range of different cancers have been demonstrated. The most effective treatment for ATO is in patients with acute promyelocytic leukemia. ATO works mainly by triggering apoptosis in cancer cells (8, 9).

Also, numerous studies have demonstrated the anti-carcinogenicity of ATO in various tumors in the body, including bladder cancer (10), ovarian cancer (11), lymphoma (12), head and neck cancer (13), and gastric cancer (14). Zhang et al., indicated that ATO can inhibit the angiogenesis and migration of gastric cancer cells by increasing the forkhead box O3 (FOXO3) gene expression in the nucleus (14). Shanmei Du et al., exhibited that ATO-treated HNSCC cells showed decreased expression of cyclin D1 protein and HPV16-E6/E7 and increased expression of pRb, p16, and p53 genes. The anti-cancer effect of ATO on HNSCCs in vivo has been confirmed by this research team (13). Dehong et al., demonstrated that ATO causes cell destruction and reduces invasive and metastatic activity in different types of cancer cells. Also, they found that ATO-treated cancer cells reduced endothelial cell tube formation in the matrigel and decreased CD31 and vascular endothelial growth factor A (VEGFA) mRNA expression, VEGFR2 expression in the VEGFA-VEGFR2-phosphatidylinositol 3-kinase (PI3K) /ERK signaling path is shown in (Figure 1). Therefore, they were able to provide guidelines for the use of ATO in the prevention of tumor angiogenesis in ovarian cancer cells (11).

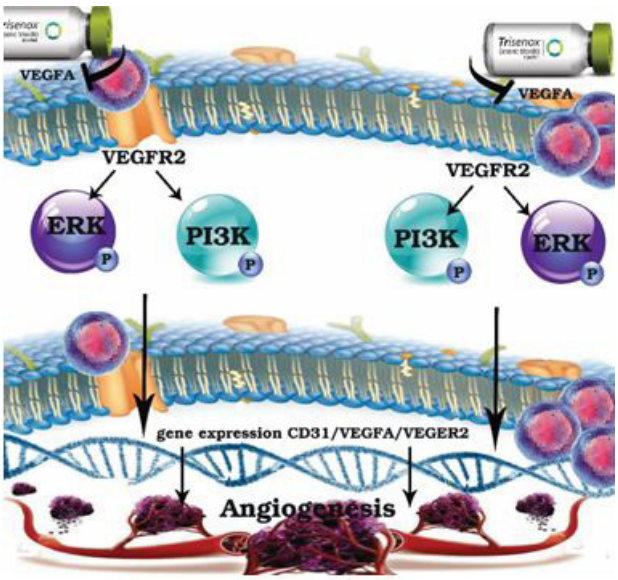

Figure 1. ATO and angiogenesis

Mechanism of ATO Effect

ATO works in different ways, some of which included ATO prompted apoptosis via re-activating the Wnt inhibitor (15), which has a selective effect at low doses on M and C2 phases (16), and acts at a high dose in a cell-cycle-independent manner, with intracellular glutathione content having an important effect on ATO-induced apoptosis (17). Also, ATO increased the expression of cellular maturation indices and induction of cell differentiation (18). Furthermore, ATO can inhibit angiogenesis by impaired VEGF production, and finally, ATO may be involved in the acetylation of histones and interfering with gene transcription (19). ATO activates epidermal growth factor receptor (EGFR) via activation of PI3K/AKT pathway in ovarian cancer cells (20). ATO inhibits the growth of MC/CAR myeloma cells by blocking the cell cycle, which is associated with the induction of cyclin-dependent kinase inhibitors, p21, CDK1, and apoptosis (21).

There are many studies on the use of ATO in the treatment of the following diseases about the mechanism of ATO effect: CML (22), CLL (23), ALL, multiple myeloma (24), AML (25), advanced hormone-resistant prostate cancer (26, 27), renal cell cancer (21), advanced cervical cancer (28), bladder carcinoma (29). The uptake of low solubility ATO in water, such as ATO, is highly dependent

on its physical properties. ATO salts are more soluble in water and more absorbent than the oxide form.

The Effects of ATO on Different Body Systems

Cardiovascular system: Inorganic ATO in low doses causes mild vasodilation and eventually edema and weight gain (30).

Effect on gluconeogenesis: ATO can induce a series of mild enzymatic and hyperglycemic changes by inhibiting pyruvate and dehydrogenase (31, 32).

Kidney Effects: Oliguria, proteinuria, and hematuria are rare ATO complications and rarely occur (31, 33).

Effects on the nervous system: The most common neurological disorder with ATO is peripheral neuropathy with dyaeathesia, a delayed complication of the drug that may occur even after discontinuation of use. This syndrome is similar to Guillain Barre's syndrome, is often reversible, and may take several months to recover (34).

Effect on the liver: Inorganic or organic ATO can cause lipid infiltration into the liver, leading to liver parenchymal injury, and ultimately increased serum glutamic-pyruvic transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), prothrombin time (PT), alkaline phosphatase (ALP), and bilirubin (35).

Effects on the digestive system: Low doses of inorganic ATO by vasodilatation and mild splanchnic hyperemia result in plasma transduction of the capillaries leading to tissue destruction and increased smoke motility and watery diarrhea. The onset of gastrointestinal symptoms may be very gradual, with nausea, vomiting, anorexia, and abdominal pain suggesting that they do not need to be discontinued consuming drugs (36).

Effect on the skin: Hot flashes, dry skin, itching, and rashes that often do not require drug withdrawal and are relieved by symptomatic treatments. Hyperpigmentation of the back, hands, and feet, and palmar hyperkeratosis occur (37).

Effect on Blood: Inorganic ATO with an effect on the bone causes blood cells to change into anemia, mild to moderate eosinophilic leukopenia, and even leukocytosis. Some of its blood complications are due to folic acid uptake disorder. ATO-induced myelosuppression was much less than cytotoxic drugs (25).

Carcinogenic and teratogenic effects: Epidemiologic evidence suggests that long-term use of ATO in drinking water or prolonged exposure to inorganic ATO may cause skin, lung, and liver cancers, but it should be noted that human studies are likely Concomitant exposure to other carcinogens has occurred and is therefore unreliable. Women of childbearing age should be advised not to become pregnant when taking ATO trioxide and it is advisable to do so with men (38).

ATO Function in Cancer Cells

ATO exerts part of its antitumor activity by inducing apoptosis by reducing the bcl- 2/bax ratio in the hl-60 cell line, without the expression of p53 (39). Researchers in the models of breast, liver, and leukemia cancers found that the ATO-ATRA compound eliminates an enzyme called Pin1. This enzyme plays a key role in regulating cancer signal transduction networks, and triggers more than 40 proteins that feed cancer tumors; this is while blocking more than 20 proteins that normally suppress tumor growth. The activity of Pin1 is overexpressed in most types of cancer, especially in cancer stem cells that drive tumor growth and can often be the key to cancer resistance to traditional therapies. When proteins other than Pin-1 are targeted for treatment, the tumor cells become resistant to treatment for some time, but if Pin-1 protein is targeted, not only the resistant tumor cell will not be treated, but also disappear the cancer stem cells (40). Maeda et al., demonstrated that in three-cell lines TSU-PR1, DU-145, and PC-3 at high and low concentrations of ATO induced apoptosis and inhibited cell growth respectively. ATO activated dose-dependent stimulation of p38, JNK, and caspase-3 genes. Maeda et al in their research indicated that ATO is a novel and safe method for the cure of androgen-independent prostate cancer (27). Feng-lian et al., in their research on human renal cell carcinoma cell line, displayed that, ATO enhances cell apoptosis and ATO can also reduce p53 and c-myc mRNA levels, and have suggested ATO as a novel functional cure for the treatment of human kidney cancer (41). In their research, Sheng Tai et al., demonstrated that specific PI3K-AKT-mTOR pathway inhibitors (Rad001) could negatively affect the development of LNCaP and PC3 cell lines in combination with ATO, and synergistically inhibits prostate cancer tumors in mice in vivo (42). Yeong-Shiau Pu et al., in their project, revealed that the combination of ATO with BSO increased cytotoxicity in bladder cancer cell lines so they introduced and suggested this medicine as a novel active drug against transitional cell cancer (43).

ATO and Prostate Cancer

Previous studies disclosed that ATO induced apoptosis and cytotoxicity effect on ovarian (MDAH 2774) and prostate cancer cell lines (DU145 and PC-3) significantly with the hydroxyanisole butylation experiments. On the other hand, they have reported that ATO has additive lethal effects with Etoposide, Cisplatin, and Adriamycin. They have also suggested to other researchers that ATO alone or in combination with chemotherapeutic remedies can be considered as a suitable and novel drug for the treatment of ovarian and prostate cancers (44, 45).

In their research, Rosenblatt et al., demonstrated that ATO

induced a dose-dependent inhibition of AR transcriptional activity in both androgen-dependent and prostate cancer cell lines. The ATO was also able to regulate the oxidative stress marker (heme oxygenase) (46).

In another study, Hui-Wen Chiu et al., indicated that ionizing radiation in combination with ATO, increased synergistic effect in treatment, reactive oxygen production, autophagy, apoptosis, and increased antitumor effects on prostate cancer cells. An androgen-sensitive and independent human (LNCaP and PC-3) becomes in vitro and in vivo, thereby inhibiting Akt/mTOR signaling pathways is shown in (Figure 2) (26). ATO prompts autophagy via the rapamycin pathway in APL cells is shown in (Figure 3) (47).

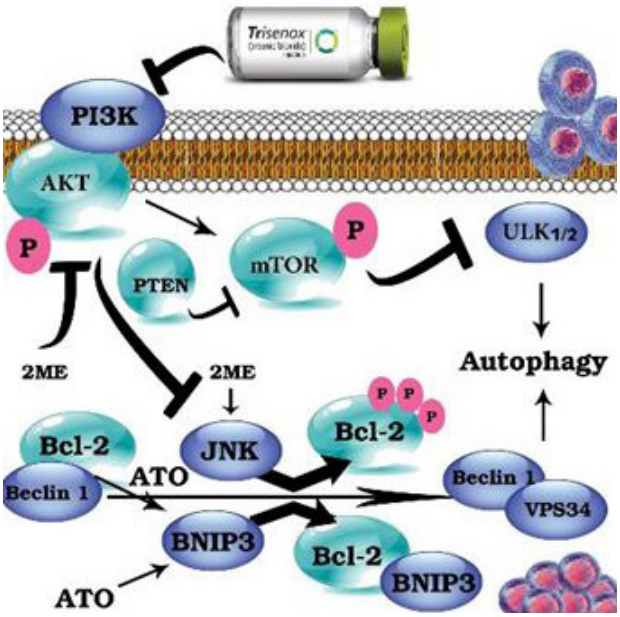

Figure 2. ATO and autophagy

ATO and Bladder Cancer

Kwong Rc et al., presented that tumors of the epidermal growth factor receptor exhibit a better response to treatment than other types of tumors. It also damages or breaks down the PML/RAR-alpha binding protein. Kwong Rc et al., has revealed in their research that treatment of bladder cancer epithelial cells with ATO as an anticancer drug is effective in combination with inhibiting glutathione synthesis. On the other hand, ATO has been shown to unfix lysosomes through p21, as well as to degrade PML/RARα protein and to inhibit cell proliferation (48). Jutooru I et al., found that ATO could significantly inhibit BIU-87 bladder cancer cell growth and DNA synthesis and induce apoptosis. Also, Bcl-2

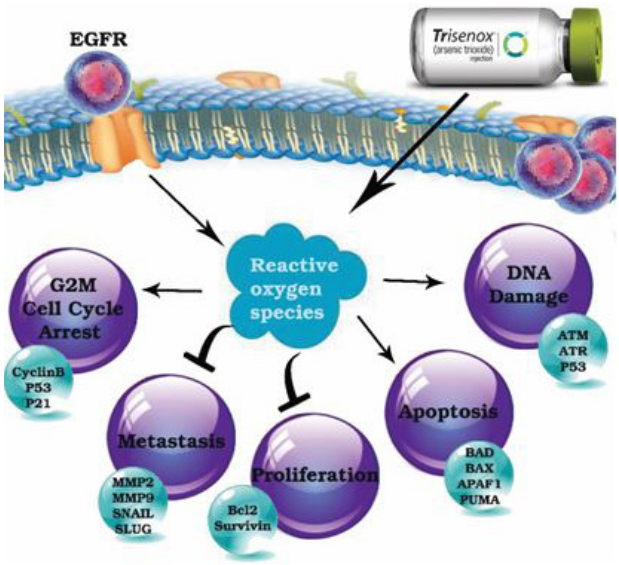

Figure 3. ATO and ROS in various functions

gene mRNA expression decreased significantly in bladder cancer cells (29). Also, ATO has been shown to induce apoptosis in addition to increasing the percentage of CD4 + and CD8 + T cells in MBT-2 (BC) bladder cancer cells and also in vivo increasing the toxicity of natural killer cells in the bladder tumor of mice (49). In vivo, Yunlong Li et al., revealed that mice treated with ATO injection showed a significant decrease in white blood cell count (WBC) and platelet count. They, therefore, suggested that injection of ATO with albumin through the internal iliac artery could be introduced as a novel and promising method for the treatment of bladder cancer (50).

Conclusions

Overall, ATO with inducing apoptosis, autophagy stimulation, growth inhibition, increasing the toxicity of NK cells, inhibiting Akt/mTOR signaling pathways, induction of cell differentiation, and inhibition of angiogenesis in different cancer cells can be concluded that ATO can be used as a potential, new and effective method, either alone or in combination with effective drugs, for the prevention and treatment of human bladder and prostate cancer.

Authors' contributions

SMKA was the principal investigator, LZB and AM wrote the mnauscript, MHKH edited the mnuscript.

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Conflict of interest
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Ethical Statement
Not applicable.

Data avaiability
Notapplicable

Abbreviations

ALP	Alkaline phosphatase
ATO	Arsenic trioxide
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal□regulated kinase
FOXO3	Fork head box O3
PI3K	Phosphatidylinositol 3-kinase
PT	Prothrombin time
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Glutamic-pyruvic transaminase
VEGFA	Vascular endothelial growth factor A
WBC	White blood cell count

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