

Role of Arsenic Trioxide in understanding its evolution in cancer defense

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Abstract

Arsenic is a well-known carcinogen that contributes to the progression of multiple cancers and has recently been reported to be one of the most effective new anticancer agents in the treatment of various cancer types, together with acute promyelocytic leukemia (APL) as well as other solid tumors. However, the effect of arsenic and its compoundson different metabolic processes are still unknown. In cancer therapy, the advancement of arsenic trioxide in the treatment of different cancers has a unique history. The glorious past of arsenic and its different forms with a significant focus on arsenic trioxide as a therapeutic approach along with the mode of action, pathogenicity, pharmacokinetics, health hazards, current clinical studies of arsenic trioxide is illustrated in this study. Besides, how arsenic strengthens its deleterious effects and how it can effectively contribute to new therapeutic developments must also be understood. Therefore an urgent need for a deeper understanding of arsenic's contradictory effect, which could have the potential to be an effective medication for different kinds of cancers. In this review, we emphasized its selective channels that would have been beneficial in focusing attention over its real role in terms of toxicity as well as potential medications for the treatment of various forms of cancer.

Keywords: Arsenic, Cancer·Solidtumor, Acute Promyelocytic Leukaemia (APL), Anticancer drug

1.Introduction

Arsenic has acquired a profile in historical memory, as suggested poison and as well as miracle medication [1], and their association among arsenic and malignancy is a mounting consensus as millions of individuals are potential victims. It has been reported that arsenic is widely distributed in the land, groundwater, fruit and vegetables, and environment as an important ecological pollutant with which living beings are routinely exposed. Arsenic discharged from both organic and man-made channels into the environment[1]. In addition to different forms of cancer such as skin cancer, bladder cancer toxic arsenic has caused various kinds of diseases[2-4]. However, arsenic trioxide is considered the most effective drug for the treatment of APL [5]. The cytotoxic potential mechanism of arsenic, as well as its methylated metabolites for cancer eradication, is woefully missing. To define the broader understanding of the toxic effects of

arsenic along with its applications in cancer treatment, caution should be taken due to limited understanding of its different toxicity exercise mechanisms.

II. Arsenic Target

In addition to different pathways, arsenic causes severely cellular alteration, particularly induced apoptosis, proliferation rate reduction, angiogenesis suppression, and differentiation stimulation [6,7]. In particular, arsenic has achieved potential success in one form of cancer called APL. In the large proportion of APL cases, the translocation that contributes to the generation of PML and RAR gene mutation is characterized (15: 17). After the effectiveness of arsenic trioxide in leukemia, specifically with a high APL success rate, the therapeutic effect of arsenic trioxide [8,9] was also investigated for other leukemia. A recent study has demonstrated that arsenic trioxide's efficacy is not restricted to hematological cancers. In vitro analysis have shown that in a variety of solid tumor cell lines such as prostate cancer, pancreatic cancer, bladder transitional carcinoma hepatoma, bladder transitional carcinoma, and breast cancer, arsenic trioxide also promotes apoptosis and proliferation arrest to demonstrate its anti-leukemic impact [10]

III. Arsenic trioxide as an agent against cancer

Arsenic trioxide is also a promising therapeutic for APL treatment and could be effective in many other cancer treatments, such as breast cancer [11-13]. A variety of solid tumor cancers, such as bladder cancer, glioma, hepatocellular carcinoma, colorectal cancer, liver cancer, cervical cancer, and lung cancer, are being studied as a principal diagnosis. Arsenic trioxide is widely reported to have a significant cytotoxic effect by rising concentrations of intracellular ROS. These reactive oxygen species induce mitochondrial membrane depolarization and activation of caspase-dependent downstream apoptosis pathways, such as caspase-3, caspase-8, and caspase-9 [14,15] transformation and unregulated proliferation of cells. Several findings have emphasized the interaction of arsenic trioxide with oncogene proteins, and abnormal signaling pathway activation, leading to progressive transformation and unregulated proliferation of cells. In controlling cell cycle progression, PML-RAR alpha is an oncogenic fusion protein that decreases the regular activities of both PML and RAR alpha [16]. Cheng et al. showed the impact of arsenic trioxide on cytokine signal transduction pathways using HepG2 [17]. Seol et al. analyzed the impact of arsenic trioxide on cell cycle progression using the head and neck cancer cell line, PCI-1 and noted that As₂O₃ persuaded G₂/M arrest in PCI-1 cells, with the association of the caspase-9 apoptotic pathway [18].

IV. The function of arsenic trioxide in apoptosis

Current investigation on myeloma cells demonstrates that caspases-9 is principally triggered in arsenic-induced apoptosis in association with dexamethasone whereas, in neuroblastoma cell lines and myeloid leukemia cells, arsenic trioxides facilitate apoptosis by triggering caspases-3. The overall mechanism through which arsenic trioxide induces apoptosis may have been inhibiting telomerase genes activity [19-22] in NB4 cells, which may be attributable to the instantaneous arsenic trioxide response to transcription factors like Sp1 and Myc.

V. Relationship between the arsenic trioxide and reactive oxygen species(ROS)

Arsenic and its associated compounds interrupt the equilibrium of natural oxidation and oxidative degradation by controlling different pathways involving several redox reactions including associated oxidants as well as other antioxidant cellular systems. As arsenic has a great affinity for thiol groups, redox-sensitive proteins with accessible and also strongly separated thiol moieties with high potential for thiol-disulfide oxidation may well be redox-sensitive and redox control facilitates significant cell functions separately.

Thioredoxin and endogenous glutathione play a key role in monitoring redox sensing and therefore shielding cells from negative impacts of arsenic therapies, it also reveals that arsenic contradictory shares several tumor promoter properties as impacts of many redox-sensitive signaling molecules like AP-1, P52, P21, and S-nitro thiols, resulting in dysfunction of different cell signaling and gene expression [23].

VI Synergist effects of arsenic trioxide in cancer protection

Breast Cancer

Breast cancer is one of the leading causes of female cancer-related mortality[24], and arsenic trioxide has a direct effect on the treatment of breast cancer. Wang et al [25] demonstrated the impact of As₂O₃ on the MCF-7 cell line. The Notch signaling pathway was extensively studied by Xia et al[26] to recognize and achieve better treatment for breast cancer in three cancer cell lines expressing the Notch genes MDA-MB-231, MCF-7, and SKBR-3. In many cancers, including breast cancer, Notch-1 plays a critical role in cell formation, invasion, and suppression of apoptosis. The abundant expression of HERG in cancer cells may perform a crucial role in the regulation of MCF-7 tumor cell proliferation. HERG levels in cancer cells treated with 8 μM of arsenic trioxide have been found to have reduced significantly.

Lung cancer

The most common form of cancer worldwide is known to be lung cancer. Walker et al.[27] have shown that arsenic trioxide causes DNA damage, cell death, and changes in protein levels associated with stress in the lung cancer cell line A549. A nonsteroidal anti-inflammatory drug, such as sulindac (arylalkanoic acid), contributes to the induction of apoptosis in lung cell lines in combination with arsenic trioxide[x]. Recent studies have also shown that the arsenic trioxide jointly with fibroblast growth factor receptor (FGFR) inhibitor PD173074 had been used to inhibit tumor proliferation in the SK-MES-1 lung squamous cell carcinoma (SCC) cell line[28]

Prostate cancer

The most common cancer in men, prostate cancer, frequently goes undetected. Many studies indicate that As₂O₃ is effective in the assassination of cancer cells. Research by Uslu et al. [29] found that cell death was noted when a dose of 10⁻⁶ M of arsenic trioxide was used on the prostate cancer cell line, and The role of p38, JNK, caspase-3, and ROS in cancer cell killing was also observed. According to another finding arsenic trioxide at low concentration resulted in inhibition of growth while caused cell death at high concentrations. Arsenic effectively inhibits

the Akt/mTOR signaling pathway, which is also an important intracellular signaling pathway in cell cycle control [30] by inhibiting PC-3 proliferation and by downregulating the Hh signaling pathway, is directly related to its anticancer approach and the antitumor activity has further enhanced by classic cyclopamine [31,32] Hh pathway inhibitor.

Cervical cancer

It is reported that the human papillomavirus (HPV) is closely associated with cervical cancer. Wen et al. have demonstrated the function of arsenic trioxide in intensifying p53 gene expression, S-G2/M phase cell cycle arrest, and activated caspase-3 expression, indicating its role in cancer cell death. Cervical cancer is among the most common cancers in women worldwide, usually managed with radiotherapy and chemotherapeutic combination therapy, like platinum-based medicines. Arsenic trioxide contributes to the downregulation of MMP-9 (Matrix metalloproteinase 9), involved in extracellular matrix degradation, and thus reduces radiation-accelerated lung metastases [33] via arsenic trioxide-mediated suppression. Including both *in vitro* and *in vivo* results indicate that treatment with arsenic trioxide-radiation has a more than predicted advantageous role in the impact of anticancer treatment on cervical cancer. In addition to arsenic trioxide, Bax protein also increases the translocation of apoptotic regulators as well as enhances the phosphorylation of Bcl-2, which eventually contributes to the up-regulation of MAPKs and JNK[34] pathways.

Ovarian cancer

The arsenic trioxide has been shown to have a cytotoxic effect on ovarian cancer cell lines (MDAH 2774) [35]. Helm et al. reported that arsenic help to overcome the resistance caused by cisplatin in ovarian cancer [36]. Besides, several studies had also been shown that arsenic trioxide caused cell death via S-phase arrest as well as consequential Fas-dependent apoptosis[37] in cisplatin-sensitive and resistant ovarian cancer cell lines. Arsenic trioxide in conjunction with CDDP (a chemotherapy drug used to treat a variety of cancers called Cisplatin) appears to be very successful and several times [38] improves the cytotoxic effect of CDDP alone. Several studies have also reported that buthionine sulfoximine and ascorbic acid can increase the efficacy of ATO by modulating GSH depletion and oxidative stress-related mechanisms in cytokine production or anticancer modulation [39,40].

VII. Conclusion and Future perspectives

Arsenic and its associated compounds especially arsenic trioxide have many mechanisms that contribute to different pathways of signal transduction that cause different cellular responses, like growth inhibition, apoptosis induction, inhibition of angiogenesis, and so many more. Arsenic compounds alone or in conjunction with several other anticancer therapeutics, like molecular targeted medications, radiation, and chemotherapy, have been shown to assist in the activation of apoptosis in many forms of cancer. There is now a possibility of targeting single molecules and signaling mechanisms as well as single cellular biological processes for a separate malignant population. Furthermore, to resolve drug resistance and improve both disease outcomes and the quality of life for cancer patients, new therapeutic agents or substitutes are desperately needed. The therapeutic double-edged sword, arsenic trioxide, began to be a poison

but has now managed to reduce a host of leukemia diseases to solid tumors. Significant numbers of clinical trials have been underway to examine the therapeutic value of arsenic trioxide in many types of malignancies and solid tumors. As arsenic trioxide has proven to have a therapeutic potential already controlled by APL in its low concentration, it is also suggested as a possible promise for other types of cancer as a preclinical model. Besides, research is needed to understand the correlation between the activation of apoptosis and genetic changes due to arsenic and its compounds in cancer cells, which could increase the selectivity of studies for cancer treatment. To develop a new combination therapy for cancer, more progress is needed to understand the synergistic anticancer activity of arsenic trioxide-based combination therapeutics.

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