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Therapeutic Role of Arsenic Trioxide in Cancer Protection

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Abstract

The growing frame of Arsenic is a significant public health concern now a day. Although arsenic is a well known carcinogen which leads to the induction of different types of cancers, it also been recently recommended as one of the most effectual novel anticancer agent for the treatment of various types of cancer including acute promyelocytic leukaemia (APL). However the exact metabolic mechanism induces due to arsenic and its compounds are still a question to be answer. The revival of this metalloid in treating APL is a unique story in cancer therapy. Based on these facts, Here we focused the effect of arsenic trioxide alone or its combination with other existing supplements in different types of cancer, and these strategies may enlightening in near future with respect to precious uses of arsenicals as medicines for treating cancer. Along with this it also requires to understand how arsenic emphasizes its toxic effects and how its implication leads to novel therapeutic advances. Hence there is an urgent need for better understanding of paradoxical effect of arsenic which may have a potential to become an appropriate treatment of various types of malignancies. Making concern in the area, in this review we focused its targeted pathways which would be helpful in shedding light on its actual role in relation to toxicity as well as in potential drug.

Keywords: Arsenic; Acute Promyelocytic Leukaemia (APL)

Introduction

Over the years, the relationship between arsenic and malignancy is much growing concern as millions of peoples are potential victims. Arsenic an environmental element, obtained a position in history, both as a recommended poison and as a miracle medicine [1]. However on the other hand inorganic arsenic (As_2O_3) is the most effective drug for the treatment of APL [2]. The mechanism of cytotoxic potential of arsenic and its methylated metabolites in eradicating cancer is sorely lacking. To describe the better understanding of the toxicity and carcinogenicity along with the use of arsenic in

chemotherapy, caution is required considering the poor understanding of its various mechanisms of exerting toxicity.

Literature Review

To provide a deeper understanding of remedial role of arsenic in cancer treatment, in this review we mainly focus on how arsenic in combination with some existing compounds mediate metabolic pathways in its anticancer potential as well as how it possess its therapeutic role for the treatment of numerous malignancies?

Potential targets of Arsenic

Apart from various pathways arsenic imposes intense cellular alteration, including induction of apoptosis, reduction in rate of proliferation, suppress the process of angiogenesis and stimulation of differentiation [3,4]. Arsenic may induces its biological effects by interacting with closely spaced cysteine residues on critical cell proteins. Arsenic achieved a potential success especially in one type of cancer called APL. In majority of APL cases, it is characterized by the t (15: 17) translocation which lead to the formation of PML and RAR gene fusion. This fusion is a representative of (19,20) transcription factor [3]. The above protein helps in the blockage of gene which is responsible of myeloid differentiation. Gene sequences of PML depicts that it has cysteine rich region which helps in arsenic interaction. This PML protein usually localized in nuclear body present inside the nucleus [5]. The interaction of PML-RAR in leukemia leads to the disruption of nuclear bodies which ultimately dispersed the PML proteins into smaller fragments. Treatment with RA also blocks the myeloid differentiation by PML-RAR fusion which implements in ATRA therapy for APL [5]. Arsenic also results in the degradation of PML-RAR fusion protein and it was proved as a novel alternative for the treatment of ATR as in both RA-resistant as well as RA-sensitive APL patients it exhibits complete abrogation [6]. Arsenic trioxide influences the promotion of a nuclear protein which colocalizes with PML in nuclear bodies and represses transcription of a gene called Daxx [7]. Daxx which have a major role in modulation of death related genes transcription in Fas induced apoptosis [8]. So a slight increase in arsenic concentration directly influences PML within nuclear bodies and sufficient to trigger Daxx-dependent apoptosis. Arsenic

and its compounds also affects the covalent modification of PML with SUMO-1 which is a ubiquitin like protein, so it involves in the augmentation of PML-containing nuclear bodies in the nucleus therefore it plays a lead role in pro-apoptotic signal transduction [9]. Hence an increasing dose of arsenic increases the SUMO-1 modification of PML-RAR and ultimately leads to apoptosis.

Response of Arsenic on cellular signaling pathways

Researchers around the country already reported that arsenic involve in pro-apoptotic pathways in several malignant cell lines that may be dependent on PML and P53. Arsenic trioxide upregulates the P53 expression in MBC-1, a B-cell lymphoma gastric cancer cells, which leads to apoptosis followed by caspase activation [10-12]. In human T-cell lymphotropic virus type 1 infected cells the increasing dose of arsenic trioxide results in the accumulation of P53, G1 phase arrest, increases the level of Cip1/p21 and p27KIP1, dephosphorylating of retinoblastoma protein and eventually leads to accumulation of P53 which induces apoptosis [13,14]. In human fibroblast cells, arsenite leads to the double strand breaks which also results in phosphorylation or upregulation of P53, so it also assist the increase in expression of P53 downstream proteins (P21 and others) [15,16]. Reports suggests that a arsenic treatment in certain extent insists P53 accumulation mainly due to the involvement of phosphatidylinositol-3-kinase related proteins, within an antaxia-telangiectasia mutated pathways [17-21] Bcl-2 have a major role in the regulation of arsenic mediated apoptosis, arsenic mainly upregulates p53, other growth arrest related genes and apoptosis while it cause downregulation of Bcl-2 in APL patients [22,23]. Arsenic modulates the binding of PML, Bax, p27KIP1 to nuclear bodies [3,24,25], along with PML containing cells, which synergistically move with IFNs (interferons) so that it prompt PML, to trigger cell death.

Effects of Arsenic

It has been demonstrated that sodium arsenite increases the activity of mutagenic components such as, c-Fos and c-Jun which eventually leads to accelerate the transcription factor-AP-1 (DNA binding activity of activator protein-1), simultaneously this AP-1 activates the JNKs which have a major role in phosphorylation of many transcription factors and enhances the expression of immediate early genes [26,27]. Arsenic mainly activates JNKs pathway by directly inhibiting the constitutive JNK phosphatase. In human embryonic kidney cells arsenic compounds activates the JNK pathway by activating MEKK3 and MEKK4 in other case without arsenic JNK activation requires activation of MEKK2 along with MEKK3 and MEKK4 [28]. Arsenic also influences the signaling pathways that are activated by increasing oxidative stress.

In bronchial epithelial cells, members of MAP kinase family which regulates the extra cellular signaling pathways also activates due to arsenic exposure [29,30]. Literature also describes that three PKC family isozymes arbitrates signal

transduction because of arsenite introduction in an epidermal cell lines which finally results in AP-1 activation [31]. So it is now almost clear that arsenic compounds have role in translocation of several PKC isoforms from cytosol to the plasma membrane, these enzymes mainly involves in mediating signal transduction and thus it may be use as a noble target for targeting biological effects of arsenic treatments. More discoveries are needed with specific inhibitors and dominant-negative mutant model helps in dissecting which MAP kinase proteins have major role in arsenic mediated action in particular cell types.

Tyrosine phosphatase

These enzymes possess vicinal thiols and hence being a potential target site for arsenic related compounds. Tyrosine phosphatase is reported as a molecular target for the activity of arsenic [32]. Some experiments also govern that due to arsenic posphotyrosine level increases but this activation causes no changes in level of tyrosine phosphatase activity.

Role in apoptosis

Arsenic trioxides have major role in caspases activation recent research on myeloma cells shows that caspases-9 is mainly activated in arsenic mediated apoptosis in combination with dexamethasone where as in neuroblastoma cell lines and in myeloid leukemia cells arsenic trioxides mediate apoptosis by activating caspases-3 the ultimate mechanism by which arsenic promotes apoptosis may be by inhibiting telomerase activity [33,34]. In NB4 cells arsenic trioxides resulted in downregulation of telomerase genes and its activity [35,36] this may be due to immediate response of arsenic-trioxide on transcription factors such as Sp1 and Myc.

Arsenic and ROS

Arsenic and its related compounds disturb the natural oxidation and oxidative reduction equilibrium by regulating various pathways involves in multiple redox reactions with intimate oxidants and other cellular antioxidant systems. As arsenic have high affinity for thiol groups, proteins with approachable as well as firmly spaced thiol moieties with high thiol disulphide oxidation potentials may be redox sensitive and redox regulation distinctly mediates important cell functions. Arsenic exerts it's both therapeutic and toxic effects by targeting redox-sensitive enzyme and proteins [37]. Endogenous glutathione and thioredoxin plays a crucial role in regulating the redox signaling and thus protecting cells from damaging effects of arsenic studies also suggests that arsenic paradoxically shares many properties of tumor promoters as effects the several redox sensitive signaling molecules such as AP-1, P52, P21 as well as S-nitro thiols which results in the dysregulation of various cell signaling and gene expression [38].

Other cellular targets of arsenic

Several reports suggests that arsenic below 10 micro molar concentration leads to the blockage of ligand binding to

glucocorticoid receptor in a region that contains a dithiol critical to proper ligand binding [39]. It also inhibits the interaction of estradiol and estrogen receptor. An arsenic compound also activates the estrogen receptor and therefore amplifies the estrogen-dependent genes. Studies also demonstrated that arsenic may act as an environmental estrogen, as in many cell types including MCF-7 arsenic induces apoptosis, this activation also inhibited by a complete antiestrogen [40]. Arsenic also acts as an antiangiogenic [41] model by disrupting the reciprocal stimulatory loop between leukemic cells and endothelial cells [42]. It negatively affects the tumour cell growth by inhibiting angiogenesis. Due to high rate of sulfhydryl content in tubulin cytoskeleton has been reported as a potential cellular target for arsenic [43]. Pyruvate dehydrogenase was earlier reported as important molecular targets of arsenic trioxide which results in the decreased gluconeogenesis and hypoglycemia. Arsenic trioxide at 5micromolar directly inhibits the activity of pyruvate dehydrogenase *in vitro*.

Synergist Effects of Arsenic with other Natural Compounds in Cancer Protection

Colon cancer

Arsenic in its inorganic form i.e., arsenic trioxide resist the activation of rapamycin: NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival, these inhibition ultimately leads to the blocking of phosphorylation as well as degradation of I κ B-alpha in HCT-116 cells [44]. This arsenic induced blocked phosphorylation of I κ B-alpha leads to apoptosis induction in colon cancer and thus possesses its therapeutic role in cancer protection. Apart from this several reports demonstrated that the combinational therapy of arsenic trioxide and PI3K inhibitor LY294002 have a drastic role in tumor reduction in colon cancer cell lines [45].

Prostate cancer

Arsenic basically inhibits Akt/mTOR signaling pathway which is an intracellular signaling pathway important in regulating the cell cycle [46]. Therefore, it is directly related to its anticancer approach by inhibiting the proliferation of PC-3 by downregulating the Hh signaling pathway and the antitumor effect was further enhanced by a classic Hh pathway inhibitor cyclopamine [47,48]. Researchers applied the synergistic therapy by combining ATO-mTOR inhibitor RAD001 which shows the induced apoptosis and autophagy rate in prostate cancer cells [49]. The induction in autophagy mediated cell death was basically linked by increased Beclin 1mRNAs stability [50,51]. So the combinational therapy of ATO-RAD001 shows much significant role in cancer suppression and tumor proliferation than monotherapy without any enhancement in weight loss.

Oral cancer

This is the most common neoplasm of neck and head which is highly associated with poor prognosis, despite of large number of treatment options are available now days. Arsenic trioxide was reported as drug additive with radiotherapy and a platinum-based anti-neoplastic drug cisplatin (CDDP), these combinations are the most appropriate therapies for oral cancer [52-54]. Several reports demonstrated that ATO +dithithreitol (DTT) leads to the increased rate of proapoptotic molecules Bax and Bak and simultaneously reduce the Bcl-2 and p53 [55], which ultimately leads to the significant cell death of oral cancer cells.

Ovarian cancer

If we talk about the rate of mortality then it is highest for ovarian cancer among all malignant tumours of female genital organs. ATO in combination with CDDP (Cisplatin a chemotherapy medication used to treat a number of cancers) proves to be much effective and it enhances the cytotoxic effect CDDP alone by many folds [56]. Many studies also notified that the effectiveness of ATO can be enhanced with buthionine sulfoximine and ascorbic acid by mediating GSH depletion and oxidative stress-related pathway in cell killing or antitumor induction [57,58].

Cervical cancer

Cervical cancer is one of the most common cancer among females worldwide, which is generally treated with radiotherapy and a combined therapy with chemotherapeutics, such as platinum-based drugs. ATO leads to the suppression of MMP-9 (Matrix metalloproteinase 9 which involves in the degradation of extracellular matrix) and thus this ATO mediated suppression decreases radiation-accelerated lung metastases [59]. Both *in vitro* and *in vivo* data depicts that ATO-radiation treatment shows more than expected beneficial role in anticancer effect on cervical cancer. Apart from this ATO also enhances the translocation of apoptotic regulators that is Bax protein and also increases the phosphorylation of Bcl-2, which ultimately leads to the activation of MAPKs as well as JNK pathways [60]. ROS has a major role in ATO-radiation-induced apoptosis [61]. Beside ATO the role of tetra arsenic *oxide* in exerting anticancer effects on cervical cancer cells has also been demonstrated. These oxides of arsenic in combination with CDDP leads to the maximum reduction of tumour growth specially in case of cervical cancer [62], this therapy also drastically increases the number of apoptotic cells and hence possess a novel anticancer role.

Breast cancer

This type of cancer is one of the leading causes of cancer related deaths among females worldwide. According to various reports it has been proven that ATO leads to reduces the expression of DNA methyltransferase-1 and induce the expression of estrogen receptor alpha, whose expression has been recognized to increase disease-free survival and indicate

an overall better prognosis [63]. Surprisingly ATO and antiestrogen tamoxifen (TAM) therapy effectively suppresses tumour growth of human breast cancer cell line MDA-MB-435 S both *in vitro* and *in vivo* [64]. Several reports demonstrated that ATO enhances the anticancer activity of rapamycin (a specific mTOR inhibitor) as well as enhances ATO-melatonin-induced apoptosis *in vivo* [65]. Various plants growth regulators such as cotylenin A (CN-A) when applied after co-incubation with ATO shows tremendous anticancer activity against breast cancer cells *in vitro* [66]. Other form of arsenic monomethylarsonous (MMaIII) and dimethylarsinous acid (DMA III) is more cytotoxic than ATO towards breast cancer.

HCC

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and the sixth most common types of cancer worldwide. Sorafenib (mutikinase inhibitors) in combination with ATO leads to induced activation of Akt [67] or its downstream factors, including glycogen synthase kinase -3beta, mTOR, ribosomal protein S6 kinase, and eukaryotic translation initiation factors 4E binding protein and extent the survival rate of patient with advanced HCC [68]. ATO also enhances the anticancer potential of metformin, survivin mutant (T34A), shikonin and andrographolide in HCC cells [69].

Lung cancer

Lung cancer is known for the most common type of cancer worldwide. A nonsteroidal anti-inflammatory drug of the arylalkanoic acid like sulindac in combination with ATO leads to the induction of apoptosis in lung cell lines [70]. This synergistic approach of sulindac and ATO mainly targets mitochondrial pathway, the NF-kB pathways as well as also mediate p53-induced downregulation of survivin and hence leads to the induction of apoptosis in lung cancer cell lines [71]. Studies also demonstrated that ATO- sulindac combinational therapy induces augmentation of cytotoxicity in both human non-small cell lung cancer cell lines (A549) by mediating ROS-induced MAPK phosphorylation via c-jun NH2-terminal kinase-dependent Bcl-xL phosphorylation [72]. Apart from this other structural analog of sulindac i.e., the nonselective cyclooxygenase inhibitors for example indomethacin was also depicts to intensify the arsenic persuaded cytotoxic outcome in A549 cells by arbitrating the exhilaration of ERK/or p38 MAPKs [73]. Recent studies also reported that the combination of fibroblast growth factor receptor (FGFR) inhibitor PD173074 and ATO suppresses tumour proliferation in lung squamous cell carcinoma (SCC) cell line SK-MES-1, here this therapy reduces FGFR1, Akt, Src, c-Raf and Erk by mediating proteasomal degradation [74]. ATO leads to ROS-mediated ER stress and mitochondrial dysfunction and ultimately leads to apoptosis in A549 cells, when it combines with resveratrol.

Gastric cancer

Anti-apoptotic drug such as ABT-737 which inhibit Bcl-2 as well as Bcl-XL when synergistically mix up with ATO leads to the

drastic suppression in the proliferation rate of human gastric cancer cell lines SGC7901 and MGC-803 [75,76].

Pancreatic cancer

Studies reported that sesquiterpene lactone such as parthenolide from the medicinal herb feverfew, enhances apoptosis of human pancreatic cancer cell lines PANC-1 and BxPC-3 by mediating ROS generation and subsequent caspase activation [77]. ATO and parthenolide significantly reduces tumor proliferation rate in PANC-1 cell line. Studies also governs that ATO alone have limited efficacy on cytotoxicity in pancreatic ductal adenocarcinoma because of the high-cellular ROS scavenging activity [78].

Glioblastoma

Arsenic trioxide increases expression of death receptor 5 (DR5), a death receptor of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) in human glioma cell lines [79]. The combination of ATO and TRAIL synergistically reduces the survival of glioma cells. Radiation therapy in combination with ATO positively regulates the autophagy effects in U118-MG cells by enhancing the mitotic arrest and modulating PI3K/Akt and ERK1/2 signalling pathways [80,81].

ATO induced apoptosis is markedly enhanced by using polyunsaturated fatty acid docosahexaenoic acid (DHA) in 12 different ATO-resistant solid tumour cell lines including breast, ovarian, colon, prostate, cervical and pancreatic cancer, without any toxic effect on normal skin fibroblasts, human microvascular endothelial cells and peripheral blood mononuclear cells derived from healthy donors [82].

Promyelocytic leukaemia (APL)

Arsenic trioxide is a chemotherapy drug and is also called Trisenox or ATO. It is a treatment for a type of acute myeloid leukemia called Acute Promyelocytic Leukemia (APL). Researchers are also looking into it as a treatment for other types of cancer. Several reports suggested that arsenic trioxide in amalgamation with all trans retinoic acid resist the cells proliferation rate as well as also induces *in vitro* apoptosis in varieties of cell types such hepatoma, breast cancer and lung cancer cells [83,84]. Apart from this Kryeziu et al. also reported that the combined treatment of erlotinib which is a selective EGFR inhibitor with ATO helps in accumulation of DNA damage by inhibiting EGFR-mediated DNA double-strand break repair in mesothelioma, hepatocellular carcinoma, colorectal carcinoma, thyroid carcinoma and cervix carcinoma *in vitro* [85].

Hematological Malignancies

Acute promyelocytic leukemia (APL)

Different reports demonstrated that the combinational therapy of As4S4 and As3+ induces the degradation of PML/RAR α oncoproteins and subsequent apoptosis [86]. Other reports emphasized that the addition of ATRA-ATO leads

to increased rate of differentiation of APL cells by inducing Src family kinase inhibitor PP2 [87]. ATO shows the antileukemic activity and this property of ATO is enhanced by the combination therapy with- granulocyte monocytes colony stimulation factor, a noncalcemic vitamin D analog 19-Nor-125 (OH)2D2,N- (beta-Element-13-yl)tryptophan methyl, Gefitinib- a selective inhibitor of epidermal growth factor receptor (EGFR) gefitinib, and high-dose vitamin C (ascorbic acid), all of which enhance ATO-induced differentiation of APL cells [88-90].

Acute myeloid leukemia (AML)

When juvenile leukocytes are augmented in an early stage of differentiation this condition is defined as acute myeloid leukemia, which is a malignant disease of bone marrow. Reports suggested that mutation in FLT3 in any AML patient have shorter internal tandem duplication (FLT3-ITD) and leads to the disease free survival [91,92]. Researchers demonstrated that the combined treatment of ATO and FLT3 specific inhibitor AG1296 induces apoptosis in FLT3-ITD –positive cells, but not in FLT3 wild type cells. Combination of ATRA+ATO exerts synergistic cytotoxicity against FLT3-ITD AML cells via co-inhibition of FLT3 signaling pathways in many APL patients [93]. These combination also induces apoptosis of NPM1-mutated AML cells by targeting nucleophosmin (NPM1) oncoprotein, whose mutation possibly represents a therapeutic targets because of high frequency in 30% AML [94]. BSO with ATO also represents anticancer effects by reducing ROS generation in AML cells [95]. In addition of BSO and ATO, dichloroacetate [96], azacytidine [97], rapamycin [98] and aclacinomycin A [99] induces apoptosis in AML cells.

Multiple myeloma (MM)

In MM cell lines relevant doses of ascorbic acid decreases GSH levels and enhances ATO-mediated cell death [100]. ATO + melphalan + ascorbic acid is one of the attractive alternative for refractory MM patients [101]. Several proteasome inhibitors such as bortezomib (BOR) and carfilzomib along with this immunomodulatory drugs such as thalidomide, lenalidomide (LEN), pomalidomide have best effect in MM patient's survival rate [102]. Reports also given a clue that enhanced cytotoxicity of ATO-BOR is associated with augmented STAT3 inhibition, JNK activation and upregulation of Bim, p21, p27, p53 as well as downregulation of Bcl-2 [103]. ATO also leads to the upregulation of cereblon which is an antimyeloma target of LEN [104], and hence increases the sensitivity of MM cells, and this sensitivity enhances by combination of ATO with vitamin E analog Trolox [105] which is a MEK inhibitor PD325901 [106] a natural quinoid diterpene cryptotanshinone and a phytochemical sulforaphane [107,108].

Lymphoma

Researchers proven that ATO with BOR shows an anticancer effects in mantle cell lymphoma which is an incurable B-cell non-Hodgkin lymphoma [109,110]. Cucurbitacin B, from

Trichosanthes kirilowii maxim, in combination with ATO synergistically enhances apoptosis rate by inhibiting STAT3 phosphorylation in Burkitts lymphoma cell lines both *in vitro* and *in vivo* [111,112].

Discussion and Conclusion

Arsenic and its related compounds twins several mechanism leads to various signal transduction pathways to effect various cellular response such as growth inhibition, induction of apoptosis, angiogenesis inhibition and many more. Here we shown that arsenical compounds, alone or in combination with other anticancer therapeutics such as molecular targeted drugs, radiation, chemotherapy helps in the induction of apoptosis in several cancer cell types. Now a days due to the advancement in technologies and surpluses of anticancer therapies there is a chance of targeting single molecules and signaling pathways as well as single cellular biological processes may generates a different malignant population of cancer cells, some of which may acquire a certain drug resistance. Therefore a novel therapeutic agents or alternatives are urgently required to overcome drug resistance and improve both the disease outcomes and the quality of life for patients with cancer. Large number clinical trials under way in several types of malignancies and solid tumour to investigate the therapeutic potential of arsenic. As arsenic in its low concentration proved to have therapeutic potential which already governed by APL and hence it is recommended as a possible promise for preclinical model of other types of cancer too. Moreover studies are required to understand the relationship between apoptosis induction and genetic changes in cancer cells due to arsenic which may enhances the studies in selectivity for cancer treatment. Further advancements are required to understand the synergistic anticancer action regarding ATO-based combination therapeutic to develop a novel combined therapy for cancer.

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