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Arsenic Trioxide: Pharmacological Applications

Trióxido de Arsénico: Aplicaciones farmacológicas

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ABSTRACT

Background: Arsenic trioxide is a chemical compound that has been used as a treatment for various diseases. Despite being potentially toxic, this compound has been used as a therapy to treat Acute Myeloid Leukemia and is being investigated as a possible treatment for different types of cancer. **Objectives**: The present review aims to describe the use and studies reported in the literature of Arsenic Trioxide as a possible therapeutic agent for Acute Myeloid Leukemia, Acute Promyelocytic Leukemia, Chronic Myeloid Leukemia, Multiple Myeloma, Myelodysplastic Syndrome, Hepatocellular Carcinoma, Lung Cancer, Neuroblastoma, Breast Cancer, Aplastic Hepatitis C, and HIV-1. **Methods:** A systematic review was conducted using databases (Elsevier, Google Scholar, PubMed) to compile documents published before December 2023. **Results:** Multiple pharmacological applications of arsenic trioxide have been reported to treat acute and chronic myeloid leukemia. Arsenic trioxide has been shown to inhibit angiogenesis, which helps treat multiple myeloma. Several studies have shown and suggested the effectiveness of arsenic trioxide as a treatment of hepatocellular carcinoma, lung cancer, neuroblastoma, prostate cancer, breast cancer, aplastic anemia, hepatitis C, and HIV-1. **Conclusion:** Despite potentially toxic effects, Arsenic compounds are therapeutic agents for multiple diseases, from syphilis to cancer. In recent years, more efficient ways have been investigated to deliver and find the specific dose to treat the disease, causing the fewest possible adverse effects.

Keywords: arsenic trioxide, pharmacological alternative, cancer, carcinoma.

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RESUMEN

Antecedentes: El trióxido de arsénico es un compuesto químico que se ha utilizado como tratamiento de diversas enfermedades. A pesar de ser potencialmente tóxico, este compuesto se ha utilizado como terapia para tratar la leucemia mieloide aguda y se está investigando como posible tratamiento para diferentes tipos de cáncer. **Objetivos:** La presente revisión pretende describir el uso del trióxido de arsénico como posible agente terapéutico para la leucemia mieloide aguda, la leucemia promielocítica aguda, la leucemia mieloide crónica, el mieloma múltiple, el síndrome mielodisplásico, el carcinoma hepatocelular, el cáncer de pulmón, el neuroblastoma, el cáncer de mama, la hepatitis C aplásica y el VIH-1. **Métodos:** Se realizó una revisión sistemática utilizando bases de datos (Elsevier, Google Scholar, PubMed) para recopilar documentos publicados antes de diciembre de 2023. **Resultados:** Se ha informado de múltiples aplicaciones farmacológicas del trióxido de arsénico para tratar la leucemia mieloide aguda y la leucemia mieloide crónica. Se ha demostrado que el trióxido de arsénico inhibe la angiogénesis, lo que resulta útil para el tratamiento del mieloma múltiple. Varios estudios han demostrado y sugerido la eficacia del trióxido de arsénico como tratamiento del carcinoma hepatocelular, el cáncer de pulmón, el neuroblastoma, el cáncer de próstata, el cáncer de mama, la anemia aplásica, la hepatitis C y el VIH-1. **Conclusión:** A pesar de tener un efecto potencialmente tóxico, los compuestos de arsénico destacan como agentes terapéuticos para múltiples enfermedades, desde la sífilis hasta el cáncer. En los últimos años, se han investigado formas más eficientes de administrar y encontrar la dosis específica para poder tratar la enfermedad, causando los menores efectos adversos posibles.

Palabras clave: Trióxido de arsénico, alternativa farmacológica, cáncer, carcinoma

1. INTRODUCTION

Arsenic trioxide (ATO) has been used as a therapeutic substance since ancient Greece and Rome more than 2,400 years ago [1,2]. Hippocrates and Dioscorides used this chemical compound to handle ulcers and control pests, syphilis, and malaria. Since the nineteenth century, it has been used to treat hematological diseases. In 1865, a patient with chronic myeloid leukemia (CML) for the first time achieved clinical remission when using potassium arsenite, for which, since that year, it was indicated as a treatment for CML [1]. In 1878, potassium bicarbonate-based arsenic trioxide solution decreased cell counts in patients with leukocythemia. In 1910, Salvarsan, an organic arsenic-based treatment, was used to treat trypanosomiasis and syphilis [2]. Also, in 1,997, the efficacy of As_2O_3 was highlighted for the remission of patients with relapsed promyelocytic leukemia (PML) [1]. In the 20th century, there was a significant decrease in the use of arsenic as a pharmacological agent; however, the U.S Food and Drug Administration (FDA) conducted several clinical trials and approved its use for patients with relapsed or refractory acute promyelocytic leukemia (APL) [2].

Despite having a potentially toxic effect, Arsenic compounds stand out as therapeutic agents for multiple diseases ranging from syphilis to cancer. Arsenic trioxide is a powerful drug for acute promyelocytic leukemia. It is being investigated as a possible pharmacological option against various types of cancer: breast cancer, glioma, liver cancer, hepatocellular carcinoma, cervical cancer, colorectal cancer, bladder cancer, and lung cancer. In order to know the antitumor effects of As_2O_3, research has focused on the activation of cell signaling pathways that can lead to cell death induced by said chemical compound [3].

2. ARSENIC TRIOXIDE

ATO's action mechanism is based on a reaction between the arsenic and thiol groups of proteins. The effect it has on cellular functions depends on three factors: cell type, duration of treatment, and dosage [54]. In APL cells, low concentrations (<0,5μM/L) induce cellular differentiation. APL cells express PML-RARα, an oncogenic protein that blocks genes related to a normal differentiation process. ATO binds to this protein and degrades it, stimulating differentiation. On the other hand, at high concentrations (0,5-2μM/L), ATO can induce dose-dependent apoptosis in APL cells, other hematopoietic cells, tumor cells, and non-malignant cell lines. The activation of the caspases cascade, the production of reactive oxygen species (ROS), and the decrease in mitochondrial membrane potential induced by the production of ROS provoke cellular apoptosis, which is closely related to the antitumor effect of ATO [54, 3]. The production of ROS also inhibits antioxidant enzymes. For example, ATO inhibits glutathione peroxidase by binding to a thiol group that is needed for its activation, or intracellular glutathione titrates arsenic, forming a complex with ATO. This results in a poor antioxidant capacity, causing cells to be prone to undergo apoptosis [54].

Furthermore, ATO has been associated with inhibiting nuclear factor kappa B (NF-κB) in malignant cells. NF-κB is a transcriptional factor that promotes cellular survival. When the inhibitor of nuclear factor kappa B kinase (IκK) phosphorylates the inhibitory protein IκB, which releases NF-κB, ATO inhibits IκK; hence, no NF-κB is released [54]. Additionally, ATO has been shown to induce autophagy by inhibiting apoptosis markers in macrophages through the transcription factor EB (TFEB), which regulates the autophagy-lysosome pathway. The production of

ROS related to ATO can induce a translocation of TFEB, promoting autophagosomal and lysosomal gene expression [55].

ATO has been well tolerated regarding adverse effects, toxicity, and safety. The most common adverse effects in APL patients were leukocytosis, gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia, and abdominal discomfort), fever, headache, cough, dyspnea, fatigue, and hepatotoxicity [54, 56, 57]. Hepatotoxicity is a common side effect due to an increased liver enzymatic activity, usually solved by decreasing the dose or interrupting treatment [56]. Skin lesions like xerosis cutis, hyperpigmentation, and erythema have been observed, but do not represent a severe or major adverse event [56, 57]. The most serious adverse events that can occur are APL differentiation syndrome (APLDS) and electrocardiography (ECG) abnormalities. APLDS refers to a group of signs and symptoms related to induction therapy for remission with ATO. It includes fever, dyspnea, hypotension, acute renal failure, pleuropericardial effusion, and lung infiltrate. It is usually treated with corticosteroids. On the other hand, ECG abnormalities commonly include prolonged QT intervals. Complete atrioventricular blockage and "torsade de pointes" type ventricular arrhythmia rarely occur. For this reason, it is recommended to monitor ECG and electrolyte levels before and during treatment with ATO [54, 56].

3. POSSIBLE PHARMACOLOGICAL APPLICATIONS OF ARSENIC TRIOXIDE

3.1 Acute Myeloid Leukemia and Acute Promyelocytic Leukemia

Acute myeloid leukemia (AML) is the most common in adults, with two incidence peaks, between 25 and 30 years old and 60 and 70 years old [4]. AML is caused by uncontrolled proliferation due to abnormal progenitor cells that accumulate in the bone marrow and blood. A block in myeloid differentiation can also cause it [5]. Arsenic trioxide has been used as first-line therapy in combination with low-dose cytarabine to treat AML; however, it should be used in low-risk patients [6].

Acute promyelocytic leukemia (APL) is a subtype of AML due to a translocation between chromosomes 15 and 17, which is t (15; 17) PML/RARA. This rearrangement will allow a blockage in the differentiation of myeloid stem cells in the promyelocyte stage [4,7].

Arsenic trioxide is an effective therapeutic agent against newly diagnosed low- or intermediate-risk APL. It is used with all-trans retinoic acid (ATRA) as first-line therapy without chemotherapy. It has been shown that this combination of drugs can cure most low or intermediate-risk patients with low or normal white blood cells and registering low toxicity. The mechanism of action of ATO is based on its effect on the leukemic promyelocyte, which is not cytotoxic. Instead, it affects various intracellular signal transduction pathways, alters the cells' function, and induces apoptosis. Among these mechanisms is the degradation of the fusion protein product of the PML/RARA gene, which causes the blocking of genes responsible for myeloid differentiation. On the other hand, ATO at lower concentrations induces cell differentiation [4].

ATRA/ATO consolidation after induction of ATRA/ATO has also been shown to achieve outstanding results in low or intermediate-risk patients [8,9]. In addition, ATO is used in patients with APL who do not respond to previous retinoid treatments or when the disease returns after other drug options have been used [10].

Some studies conducted in China and the United States showed that ATO could induce sustained molecular remission, being used as monotherapy in patients who suffer a relapse after treatment containing ATRA; later, other studies confirmed these findings. [11]

According to the European Medicines Agency, in the induction phase, ATO should be administered every day until it is verified that the drug is working, which means that the cancer cells have been eliminated from the bone marrow. The treatment should be interrupted if it is not achieved before day 50 or 60. It can also be used for the consolidation phase, where it should be given once a day for five days, then a 2-day break, which is repeated for 4 to 5 weeks [10].

Some side effects that may arise after the use of this drug are dyspnea, fever of unknown origin, unexplained weight gain, hypotension, acute renal failure, the appearance of pulmonary and pericardial edema [12], headaches, fatigue, arthralgia, myalgia, bone pain, itching, hyperkeratosis, skin hyperpigmentation, exfoliative dermatitis, inflammation of the mucous membranes of the eyes, nose, mouth and digestive tract, abdominal cramps, diarrhea, hypokalaemia, hypomagnesemia, elevated transaminases, segment prolongation QT on the electrocardiogram and sudden deaths [1].

3.2 Chronic Myeloid Leukemia

Another disease that can be treated through ATO is chronic myeloid leukemia (CML). CML is a myeloproliferative neoplasm originated from the acquisition of the BCR-ABL fusion gene associated with t 9;22) (q34; q11) [13]. Specifically, the main cause of CML is believed to be a chromosomal abnormality in a chromosome called Philadelphia (Ph1), the result of a reciprocal translocation in a single fusion gene, called BCR-ABL, that is a mutation formed by the combination of two genes (the BCR and the ABL). [14,15]

From a pathophysiological point of view, the BCR-ABL gene is distributed throughout the cytoplasm and interacts with proliferation, differentiation, and survival functions [13]. This generates interferences in the MAPK mechanisms (which causes an expansion of the tumor clone), in the PI3K pathway (which suppresses programmed cell death), and in focal adhesion components, which decreases cell adhesion, among others [13]. In addition, its medullary microenvironment is characterized by factors such as the reduced capacity to support normal hematopoiesis, protection against apoptosis, and induction of resistance mediated by cytokines and cell-cell interactions [13]. Likewise, there is a vascular endothelial growth factor (VEGF) which is associated with the growth of cancerous tumors and contributes to the pathogenesis of chronic myelogenous leukemia (CML) since it has been found that the BCR-ABL gene that causes CML also increases VEGF [16].

For its treatment, molecularly directed therapies based on tyrosine kinase inhibitors [14] are used, which block the mechanism of enzymatic action of the BCR-ABL gene fusion protein and are successful in most cases. Those therapies that are based on the use of tyrosine kinase inhibitors such as imatinib mesylate; however, resistance to this drug tends to be developed, both due to intrinsic factors (such as mutations in the same fusion gene or clonal evolution) and extrinsic factors (lower bioavailability of the drug) [13]; therefore, the ATO can also be used for the treatment of CML.

Various investigations [17,18] mention that ATO and other drugs used to treat CML have side effects such as thrombocytopenia and bleeding, which in some cases are the leading cause of death in some patients with this type of leukemia. For this reason, more efficient ways have been investigated [18] both to deliver this drug to patients and to find the specific dose so that the disease can be treated in this way. For example, it is known that drug treatments that have combinations of ATO with imatinib can eliminate CML-initiating cells. In contrast, the same treatment without implementing ATO (only with imatinib) did not show positive results and did not achieve the goal of curing the disease [19].

Also, ATO can be combined with tretinoin (all-trans-retinoic acid or ATRA) to give complete remission results more significant than 90% in the treatment of CML or with idarubicin for induction therapies [20]. The ATRA/ATO combination induces the differentiation of leukemic promyelocytes into mature granulocytes, and this combination also reduces relapse rates compared to treatments with these compounds individually. Furthermore, ATRA/ATO has lower hematological toxicities and significantly improves survival in CML patients with chemotherapy [21].

Another relevant investigation focused on human serum albumin (HSA) nano-drug labeled with folate (FA) and loaded with ATO, called FA-HSA-ATO. This nano-drug could specifically recognize folate-β-positive receptors (FRβ +) in CML cancer cells resulting in a higher intermolecular concentration of ATO, verified by *in vitro* experiments, which can increase the efficacy of this drug and decrease its side effects [17].

3.3 Multiple myeloma

Multiple myeloma (MM) is a malignant neoplasm of clones of plasma cells. MM is characterized by the production of monoclonal proteins, kidney diseases, plasmacytosis in the bone marrow, bone lesions, anemia, immunodeficiency, and hypercalcemia. The evolution of MM will depend on genetic changes in tumor cells and conditions that favor a suitable microenvironment in the bone marrow for cancer cells [22].

Arsenic trioxide has been used as a treatment for MM since it activates procaspase-3, which generates apoptosis in MM cell lines by degrading the tumor necrosis factor receptor inactivating protein. Furthermore, it induces cell cycle suspension by triggering apoptosis via caspase-3 and inducing the cyclin-dependent kinase inhibitor protein p21 [23]. Also, ATO has been shown to inhibit angiogenesis, which is very useful for treating MM. It has been proposed as a mechanism of action that ATO interrupts the intrinsic apoptosis pathways since it generates reactive oxygen species (ROS) and blocks the redox enzymes of reduced glutathione, thiol transferase, and glutathione (GSH) peroxidase.

In addition, phase I and II clinical trials were conducted in patients with this disease who are in a relapsed or refractory stage with intensive pretreatment. It should be noted that using ATO as a treatment for multiple myeloma has had limited success in patients who are in refractory MM since they achieve more excellent resistance of tumor cells to ATO due to the changes that this drug causes in the levels of GSH and other regulators that have the function of apoptosis [24]. Other studies have shown that ATO administration in combination with other anti-MM drugs (bortezomib, DNA methylation inhibitor 5-azacitidine, and melphalan) causes a synergistic effect.

3.4 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary neoplasm in the liver. This type of cancer mainly affects people with chronic liver diseases caused by liver cirrhosis, which is due to the hepatitis C virus, the hepatitis B virus, or alcohol. HCC is the most common cause of death in patients with liver cirrhosis [26,27]. Transcatheter hepatic arterial chemoembolization (TACE) is the first-line treatment for patients with primary hepatic carcinoma since it does not have as many adverse effects, has a curative effect, and is easy to establish collateral circulation. However, repeated treatment can worsen liver damage because it can cause ischemia and hypoxia, leading to increased vascular endothelial growth factors in tumor tissues. For this reason, arsenic trioxide has been used as an alternative in conjunction with TACE for the curative treatment of this type of cancer since they demonstrated an improvement in the clinical efficacy rate, improving the quality of life of patients, increasing their one-year survival rate, and reducing the side effects caused by chemotherapy [28].

Another randomized, single-blind, two-parallel-group study was conducted in three medical centers with 139 patients with biopsy-confirmed HCC and lung metastasis. This study evaluated the safety and efficacy of transarterial chemoembolization with arsenic trioxide and intravenous administration in unresectable HCC with lung metastasis. As a result, it was obtained that intravenous infusion with ATO has a better therapeutic effect, the survival time of the patients was increased, and there were no serious adverse effects, so it was possible to conclude that this treatment is safe and effective for people with HCC with lung metastasis [29]. Another study with 24 patients with HCC was conducted to investigate the effects of arsenic trioxide treatment on ezrin expression and serum alpha-fetoprotein (AFP) levels in this type of cancer. Ezrin expression is essential in the invasion of tumor cells, and its expression level is related to the development, metastasis, and prognosis of tumor cells. As a result of this study, it was obtained that the expression of the ezrin gene was reduced after using arsenic trioxide as a treatment; it was also possible to show that it can significantly decrease the levels of AFP in serum, which is why it is considered a potent inhibitor of the growth of cancer cells [30].

3.5 Lung cancer

Lung cancer is one of the most severe diseases, with one of the highest incidences in humans and a high rate of oncological mortality globally. Furthermore, it is the leading cause of cancer mortality in men and the third in women [31]. A study hypothesized that arsenic trioxide has bioactivity against lung cancer, and its mechanisms of action are through cell damage, apoptosis, and changes in proteins related to stress in tumor cells. The research indicated that arsenic trioxide causes toxicity in lung carcinoma cells (A549), and oxidative, apoptotic, and genotoxic mechanisms can produce these effects. In addition, it is suggested that arsenic trioxide may be a potential chemotherapeutic agent for treating this type of cancer; however, it is necessary to carry out more *in vivo* studies with animal models of lung tumorigenesis to confirm the therapeutic effects of arsenic trioxide [32].

3.6 Neuroblastoma

Neuroblastoma (NBL) is an extracranial tumor characterized as an embryonal neoplasm that affects the development of the paravertebral sympathetic nodes and the adrenal medulla in children [33,34]. Arsenic trioxide has been used as a possible treatment for NBL since it stops the cell cycle of tumor cells in the G2/M phase. A study suggests combining chemotherapeutic drugs with arsenic trioxide can improve the effectiveness of cytotoxic effects against neuroblastoma. It is essential to mention that the order of application of the drugs is a fundamental factor since the study showed that preincubation with arsenic trioxide followed by a specific agent of the mitosis phase could achieve a greater effect against cancer compared to the application single-drug or followed by a phase-specific non-mitosis agent [35].

3.7 Prostate cancer

Prostate cancer is a hormone-dependent neoplasm that is the second leading cause of death in men worldwide. Its prevalence increases after age 50; this disease is not so frequent before this age. It is considered a "silent disease" because ten years can go by without symptoms as cells grow and transform. Prostatic carcinoma is a malignant tumor derived from the acinar and ductal epithelium of the prostate that can vary considerably in its glandular differentiation, anaplasia, behavior, metastatic patterns, and response to treatment [36].

The growth rate of prostate carcinoma tumors ranges from very slow to moderately rapid. Some patients may have prolonged survival even after cancer has metastasized to distant sites such as bone. Arsenic trioxide kills prostate carcinoma cell lines in culture and has significant antitumor activity in an androgen-independent murine model of prostate cancer. In a phase II trial of arsenic trioxide in patients with advanced hormone-refractory prostate cancer, the prostate-specific antigen (PSA) levels in two of the 15 evaluable patients were markedly reduced, and the rise in levels was reduced in another 12 patients. [37].

An *in vitro* study was conducted in LNCaP cells (androgen-sensitive human prostate cancer cells) and PC-3 cells (androgen-independent human prostate cancer cells) to investigate the anticancer effects of ionizing radiation combined with Arsenic Trioxide. The combined treatment induced autophagy and apoptosis in LNCaP cells and mainly induced autophagy in PC-3 cells. The results obtained *in vitro* were supported by *in vivo* experiments using mouse models with PC-3 cell xenograft tumors; the combined treatment suppressed tumor volume and weight in nude mice compared to treatment with Arsenic Trioxide or ionizing radiation alone. Furthermore, the combination therapy resulted in a 74% tumor growth inhibition. The cell death observed in the *in vitro* study induced by the combination treatment was primarily the result of the inhibition of Akt/mTOR signaling pathways. These findings suggest that the combined treatment of Arsenic Trioxide and ionizing radiation is a potential therapeutic strategy for androgen-dependent prostate cancer and androgen-independent prostate cancer [38].

3.8 Breast cancer

Breast cancer is the malignant proliferation of epithelial cells that line the ducts or lobules of the mammary gland. It is a disease that affects mainly older women; 75% of cases occur in women over 50. The female: male ratio is 150:1; it is a hormone-dependent disease [39].

In order to investigate the possible therapeutic application of As_2O_3 in breast cancer, the effects of As_2O_3 on the growth of four human breast cancer cell lines were analyzed: MCF7, MDA-MB-231, T-47D, and BT-20. The susceptibility to the direct apoptotic effects of $As_2O_3$was analyzed; in addition to evaluating the signs of cell differentiation, the expression profile of ICAM-1 (CD54) was evaluated, and the consequences of treatment with As_2O_3 on the immunogenicity of tumor cells and the effector cells of the immune system. This study demonstrated by standard cytotoxicity assays that As_2O_3treatment can increase the lysis of breast cancer cells by lymphokine-activated killer cells (LAK cells) and demonstrate an important role for the ICAM-1/LFA-1 interaction in this process. As_2O_3induced varying degrees of differentiation, apoptosis, and lysis in these model cell lines and may be a promising adjuvant to current breast cancer treatments by its apoptotic, differentiating, and immunomodulatory effects [40].

An *in vitro* study evaluated the effects of As_2O_3 on the growth of two ER-positive breast cancer cell lines: MCF7 and T47D. It was found that at high doses of As_2O_3, the survival of the two ER-positive breast cancer cell lines, MCF7 and T47D, was reduced, while lower doses of As_2O_3 significantly inhibited the expression of the estrogen receptor alpha (ER-alpha), but they did not affect ER-beta expression. ER-alpha expression is fully restored when As_2O_3 is absent for 24 hours. As_2O_3 strongly repressed 17-beta-estradiol (E2)-stimulated transcriptional activation. Furthermore, As_2O_3 abolished E2-mediated transcriptional induction of the estrogen-sensitive gene pS2. These results indicated that As_2O_3 specifically inhibits the ER-alpha signaling and expression pathway. As_2O_3, in combination with other methods, could provide a new therapeutic approach for ER-alpha-positive breast cancer [41].

A study was conducted on breast cancer patients in which the combined effect of topical As_2O_3 and radiotherapy on fungal and infiltrating skin lesions of breast cancer was examined. According to the results of this investigation, significant systemic absorption of As_2O_3 was not determined from a pharmacokinetic study; in addition, a decrease in wound secretion and an improvement in local tumor control were observed, as well as other benefits that

include the drying of skin lesions and reduction of unpleasant odor. As_2O_3 can stop the cycle of tumor cells in the G2/M phase, the tumor cells being more sensitive to radiation at this stage of the cycle can produce sensitization of tumor cells to radiation [42].

Combining As_2O_3 and radiation therapy offers a practical, tolerable, and safe treatment modality for the palliative care of breast cancer patients with superficial malignant lesions. Although the results of this pilot study are promising, the limitation of the small number of patients enrolled and the lack of a specific comparison with the efficacy of solar radiation makes necessary further randomized phase III trials [42].

3.9 Aplastic anemia

Aplastic anemia is a pathology with pancytopenia and a reduction in hematopoietic stem cells in which hematopoietic tissue is exchanged for adipose tissue. This disease is one of the anemias considered regenerative [43]. Aplastic anemia is caused by an over-activation of T lymphocytes that target the bone marrow. Cytotoxic CD8 T cells that are over-activated attack hematopoietic progenitors and stem cells, generating excessive apoptosis [44].

Arsenic trioxide favors the expression of the BMP4 gene in stem cells from patients with aplastic anemia, which decreases differentiation into adipose cells and increases differentiation into osteoblasts [45]. In addition, a study was conducted in patients with severe aplastic anemia where a dose of 0.15 mg/kg was administered intravenously daily for five days every week for eight weeks. This study demonstrated that arsenic trioxide helps to improve hematopoiesis in severe refractory aplastic anemia since it could regulate adipogenic and osteogenic differentiation of mesenchymal stem cells (MSCs), inhibiting adipogenic differentiation and enhance osteogenic differentiation of MSCs. [46]. Likewise, it was shown that arsenic trioxide could collaborate in immune regulation since it regulates the percentage of Tregs and can decrease the levels of IFN-γ, IL-4, IL-17, and TGF-β1 in the peripheral blood of patients with severe aplastic anemia [44].

3.10 Hepatitis C

Hepatitis is an inflammation of the liver, with an irregular degeneration of parenchymal cells, the necrosis of liver cells, and a lobar inflammatory reaction and disruption of the hepatocyte cords. These alterations cause Kupffer cell hyperplasia, cellular degeneration, and periportal infiltration by mononuclear cells. Hepatitis C (HCV) is mild, with a minimal elevation of liver enzymes. Patients with this disease usually do not require hospitalization, and jaundice only occurs in less than 25% of people with hepatitis C. Yet, many patients may develop cirrhosis and are at high risk for hepatocellular carcinoma [47].

Multiple antiviral trials demonstrated that arsenic trioxide in sub-micromolar concentrations could inhibit the replication of the hepatitis C virus. It was shown that combining interferon-alpha and arsenic trioxide can generate synergistic effects against HCV. Likewise, ATO and IFN-alpha can synergistically induce a negative regulation of genes involved with the cell cycle, which causes it to stop and generate apoptosis of cells. The anti-HCV activity of arsenic trioxide has been verified through various assays using Ava5 cells that have the subgenomic HCV RNA replicon. Furthermore, it was shown that ATO could completely abolish the signal of the hepatitis C virus in an alternative replication system of the virus [48].

3.11 HIV-1

HIV-1 is a retrovirus of the lentivirus family, composed of two identical copies of single-stranded RNA molecules. It invades cells containing specific membrane receptors and incorporates a DNA copy into the host genome. HIV-1 is acquired by contacting infected body fluids, particularly blood, and semen. The most common modes of transmission are sexual, parenteral (recipients of blood or blood products, injection drug users, and occupational exposure to contaminated products), and vertical transmission (mother to fetus) [49].

One study demonstrated that arsenic trioxide reactivates latent provirus in CD4+ T cells of HIV-1 patients and simian immunodeficiency virus (SIV) infected macaques without significant systemic T cell activation and no inflammatory responses. Arsenic trioxide combined with antiretroviral therapy (ART) delays viral rebound after ART termination, reduces integrated SIV DNA copies on CD4+ T cells, and restores CD4+ T cell counts *in vivo* [50,51].

Half of the arsenic trioxide-treated macaques showed no detectable viral rebound in plasma for at least 80 days after antiretroviral therapy was stopped. CD4 receptors and CCR5 coreceptors on CD4+ T cells are significantly down-regulated by treatment with arsenic trioxide, which reduces susceptibility to infection after provirus reactivation. Furthermore, increased SIV-specific immune

responses after treatment with arsenic trioxide may suppress viral rebound [51].

3.12 Myelodysplastic syndrome

Myelodysplastic syndrome is a hematologic disease characterized by a clonal disorder, where dysplasias are observed in one or more cell lines and ineffective hematopoiesis, and there is an increased risk of developing acute myeloid leukemia [52]. Patients' most common symptoms are related to cytopenias, including infections, fatigue, and bleeding. Most patients will need red blood cells or platelet transfusions during the condition [53].

Some *in vitro* studies demonstrated apoptosis in cells with Myelodysplastic syndrome exposed to As_2O_3. Cells with Myelodysplastic syndrome are subjected to more significant oxidative stress, which leads to the possibility of having sensitivity to As_2O_3. In two phase II clinical studies involving 191 patients, As_2O_3 as a single agent was associated with a hematological improvement in 26–34% of patients with lower-risk Myelodysplastic syndrome and 6–17% of those with higher-risk Myelodysplastic syndrome [54].

In addition, As_2O_3 was investigated together with thalidomide based on the hypothesis that this combination would target both the myelodysplastic syndrome clone and the bone marrow microenvironment. This combination was evaluated in patients with a myelodysplastic syndrome, where it was observed that patients with high baseline levels of the EVI1 marker responded to the combination; later, this observation was supported by *in vitro* experiments, which demonstrated greater sensitivity to As_2O_3 in cells expressing high levels of EVI1. [54]. A phase II study evaluating the safety and efficacy of this treatment was also conducted, where most of the adverse effects observed were mild or moderate, and there were no treatment-associated deaths [53].

CONCLUSIONS

Despite having a potentially toxic effect, Arsenic compounds stand out as therapeutic agents for multiple diseases ranging from syphilis to cancer. Arsenic trioxide (ATO) has been used as a therapeutic substance since ancient Greece and Rome for more than 2,400 years, but since the 19th century, it has been used to treat hematological diseases.

Arsenic trioxide is a potent drug for acute promyelocytic leukemia and is being investigated as a possible pharmacological option against various types of cancer: breast, glioma, liver cancer, hepatocellular carcinoma, cervical cancer, colorectal cancer, bladder cancer, and lung cancer. In order to know the antitumor effects of As_2O_3, research has focused on the activation of cell signaling pathways that can lead to cell death induced by said chemical compound.

Some side effects that may arise after the use of this medicine are: dyspnea, fever of unknown origin, unexplained weight gain, hypotension, acute renal failure, the appearance of pulmonary and pericardial edema, headaches, fatigue, arthralgia, myalgia, bone pain, pruritus, hyperkeratosis, skin hyperpigmentation, exfoliative dermatitis, inflammation of the mucous membranes of the eyes, nose, mouth and digestive tract, abdominal cramps, diarrhea, hypokalaemia, hypomagnesemia, elevated transaminases, QT segment prolongation in the electrocardiogram and sudden deaths; Due to the above, in recent years, more efficient ways have been investigated both to deliver this drug to patients, and to find the specific dose so that in this way the disease can be treated causing the fewest possible adverse effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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