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A Review of Arsenic Trioxide in the Treatment of Acute Promyelocytic Leukemia: Clinical Efficacy, Toxicity, and Future Directions

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Abstract

Acute promyelocytic leukemia (APL) is a severe and life-threatening form of leukemia characterized by unique genetic and chromosomal abnormalities, often leading to fatal complications such as hemorrhage and embolism. Arsenic trioxide (ATO) has become a key therapeutic agent for APL, achieving high remission rates, including in patients with relapsed disease, and offering advantages over other treatments such as bone marrow transplantation and all-trans retinoic acid (ATRA). This review examines the chemical and pharmacological properties of ATO, its mechanisms of action in APL treatment, and its clinical efficacy and toxicity based on studies conducted worldwide. Additionally, this review explores potential applications of ATO beyond APL and discuss future research directions to expand its therapeutic scope in clinical settings.

Keywords: arsenic trioxide, APL, physicochemical property, clinical application

1. Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute leukemia characterized by specific genetic and chromosomal karyotype abnormalities, which can result in severe clinical manifestations, including high fever, infections, anemia, and tissue infiltration (Hong-Hu Zhu, Jiong Hu, Francesco. Lo-Coco & Jie Jin, 2019). In addition to these symptoms, extensive hemorrhage and embolism are common complications and the primary causes of mortality associated with APL (A. Lykknes & L. Kvittingen, J, 2003). ALP is easy to find in young and middle-aged people, and the average age of onset is 39 years old (Hematology Branch of China Medical Association, Hematology Branch of Chinese Medical Doctors' Association, 2014). Epidemiological studies have confirmed that the incidence of APL accounts for 5.0%-23.8% of leukemia in the same period, and 6.2%-40.2% of acute myeloid leukemia (AML) (Gan Ge, Sun Jun, Wang Jiayu, et al, 2008).

Among the research focused on the clinical treatment of APL, arsenic trioxide (ATO) has been found to have not only a high rate of complete induction of remission, but also a good effect for a wide range of APL patients, including relapsed patients; compared with bone marrow transplantation which is only suitable for high-risk or refractory relapsed APL patients, or all-trans retinoic acid (ATRA) which has a high cure rate after initial treatment but a

poor treatment effect for relapsed patients (Woo SH, Park IC, Park MJ, Lee HC, Lee SJ, Chun YJ, et al, 2002). ATO established its position in the medical field in after Hu Xiaochun (1992) et al., a researcher at Harbin Medical University in China, put the drug into use in the treatment of APL and achieved successful results (C.R. Kumana, W.Y. Au, N.S. Lee, M. Kou, R.W. Mak, C.W. Lam & Y.L. Kwong, 2002). Following the subsequent successful validation of the efficacy of ATO for the treatment of APL in randomized clinical trials in the United States, the Food and Drug Administration (FDA) approved ATO in September 2000 as a Trisenoxt (ATO Injection) for the treatment of APL. Similarly, Trisenoxt was also approved by the European Agency for the Evaluation of Medical Products (EMEA) in 2002 for the treatment of APL (H. D. Sun, L. Ma, X. C. Hu & T. D. Zhang, 1992). Since then, researchers have been trying to explore the undiscovered role of ATO in clinical treatment and clarify its molecular mechanism.

This article comprehensively reviews the application of ATO in clinical treatment and its possible prospect. Specifically, this article will first review the chemical and pharmacological features of ATO, then summarize its mechanisms in the treatment of APL. Following this, the clinical efficacy and adverse effects of ATO reported in studies from different countries over the years will be summarized and compared. Finally, the article will explore the potential applications of ATO beyond APL and discuss areas of potential development for future research.

2. Chemical and Pharmacological Properties of Arsenic Trioxide

ATO is a trivalent oxide of arsenic with the chemical formula of As_2O_3, also known as arsenic oxide, commonly known as arsenic, white arsenic, etc. (Hushes M, 2009). It is odorless and tasteless white powder, highly toxic, the most commercially valuable arsenic compound, and one of the oldest toxicants. It has monoclinic, cubic and amorphous forms, and its melting point and boiling point are slightly different with the crystal form. In industry, arsenic sulfide slag is usually prepared through leaching with sodium hydroxide solution, air oxidation desulfurization and SO_2 reduction. According to the pharmacokinetic analysis by Ni et al. (Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al, 2001). On APL treatment by intravenous infusion of ATO through gas chromatography, and monitoring of urine arsenic excretion and terminal arsenic accumulation, under the condition of intravenous infusion of 10mgATO injection for two hours, the peak blood concentration C_{pmax} was 0.94±0.37 mg/L, peak reaching time T_{peak} was four hours, and the plasma concentration distribution half-life $t_{1/2\alpha}$ was 0.89±0.29 hours. The elimination half-life $t_{1/2\beta}$ was 12.13±3.31 hours, the systemic clearance CL_S was 1.43±0.17 L/h, the apparent distribution volume V_c was 3.83±0.45 L, and the area under the concentration-time curve (AUC) was 7.25±0.97mg.h/L/L. Pharmacokinetic parameters were generally consistent with continuous dosing. During the treatment, the 24-hour urinary arsenic excretion was 1%–8% of the daily dose, and the accumulation and rise of peripheral arsenic was more significant, reaching 5-7 times before medication at the highest. Urinary arsenic excretion and terminal arsenic accumulation began to decrease gradually after drug discontinuation. The excellent pharmacokinetic characteristics and physicochemical properties of ATO have laid the foundation for its becoming a clinical treatment of APL (Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al, 2001).

3. Mechanism of Arsenic Trioxide in Treatment of APL

APO is one of the major clinical treatments for APL. APL has a unique model system in cancer biology. The unique ectopic chromosome aberration t(15, 17) is the main genetic abnormality in most patients with APL. The occurrence and expression of this aberration is the promyelocytic leukemia (PML) gene fused with retinoic acid receptor α(RARα) gene, which leads to the translation of PML/RARα chimeric protein and blocks the differentiation of hematopoietic progenitor cells. It finally leads to the occurrence of APL (Dbaibo GS, Kfoury Y, Darwiche N, Panjarian S, Kozhaya L, Nasr R, et al, 2007). The main therapeutic mechanism of ATO on APL is to target and induce the degradation of APL-specific PML/RARα oncogenic fusion protein and lead to cell differentiation (Niu Yimin, Cherokee Sakurai, Sun Hui & Wang Xijun, 2011). ATO has a high binding affinity for cysteine residues in PML, which may be the beginning of degradation leading to PML/RARα. Regarding the molecular mechanisms of arsenic-induced degradation of the PML/RARα fusion protein, it is believed that

ATO directly binds to the PML or the ring of the PML moiety in the PML/RARα fusion protein and the zinc finger motif in B1-case, causing their multimerization and conformational changes, followed by interaction with the unique SUMO (small ubiquitin-related modifier) E2-ligase UBC9 to enhance the SUMO of these proteins. In addition, the SUMO-derived PML or PML/RARα protein further recruited its chaperonin such as DAXX, SP100, CPB and RNF4 (a SUMO-dependent E3 ubiquitin ligase), and finally promoted the degradation of PML or PML/RARα fusion protein through the ubiquitin-proteasome pathway (Lin Shufen & Chen Ruquan, 2004). In addition to relying on the proteasome degradation pathway, autophagic lysosomes were also found to play a role. The destruction of PML-RARα unblocked the differentiation of APL by overcoming the dominant negative effect of the fusion protein on the normal function of PML and RARα. Differentiation antigens CD11b and CD33 are also regulated to some extent during cell maturation. Besides the most important differentiation induction, the therapeutic mechanism of ATO also has the most direct cytotoxic effect and induction of apoptosis. It may induce the decrease of cell mitochondrial transmembrane potential, activate caspase 3 and finally cause the apoptosis of tumor cells. Vascular endothelial growth factor (VEGF) is highly expressed in bone marrow cells of patients with chronic myeloid leukemia (CML), and it may also inhibit CML cell growth by inhibiting VEGF expression and blocking angiogenesis. The experimental study by Lin Shufen et al. (2004) showed that arsenic compounds could combine with sulfhydryl group (-SH) in tissue protein to inactivate sulfhydryl-containing enzyme and inhibit excessive cell proliferation. In addition, arsenic can inhibit the proliferation of tumor cells or cause their death by interfering with the energy metabolism of mitochondria. In addition, it can also damage the cell membrane, causing the loss of the synthesis of cellular DNA and RNA as well as the clonal proliferation ability, thus achieving the effect of combating poison with poison (Sun Hong, Ma Liang, Hu Xiao & Zhang Tailin, 1992). As a result, the ability of ATO to target induction of differentiation and apoptosis as well as certain cytotoxic effects have made it possible to become an effective therapeutic regimen clinically.

4. Clinical Study and Efficacy Evaluation of Arsenic Trioxide

The efficacy of ATO in APL treatment has been widely studies across the world. For instance, Zhang et al. (1992) from China conducted the first experiment of ATO treatment for relapsed APL and they observed that ATO could induce complete remission in 72% of patients (Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, et al, 1997). In addition, experimental data from Xiong et al. (1997) showed that the complete remission rate of ATO in the treatment of recurrent APL was 90% (Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al, 2001). Another study from the US found that recurrent APL achieved a complete remission rate of 92% in the sample of patients, and PML/RARα disappeared in 8 of 11 patients (Soignet SL et al., 2001; Alimoghaddam K, Ghavamzadeh A, Jahani M, Mousavi A, Iravani M, Rostami S, et al, 2011). In a multicenter study of APL relapsed after first-line treatment with ATRA and chemotherapy, 40 patients received 0.15mg/kg ATO until the disappearance of abnormal promyelocytes and myeloblasts in bone marrow and peripheral blood. A complete response was observed in 85% of patients, with a median time to complete response of 59 days (YL Kwong, WY Au, CS Chim, A Pang, C Suen & R Liang, 2001). Similarly, Alimoghaddam et al. (2014) studied 31 patients with relapsed APL with ATO having a mean age of 27 years and a mean white blood cell count of 2000/mm3 (500-44000). ATO was infused at a dose of 0.15mg/kg/d until abnormal cells in the bone marrow disappeared. Complete remission was observed in 77% of treated cases, and four patients died during the remission induction phase. In patients with complete remission, 10 relapsed. In these cases, the 2-year LFS and OS were 54.6% and 81.1%, respectively.

ATO is commonly used in clinical ATRA and APL relapsed after chemotherapy. The therapeutic mechanism of ATRA is similar to that of ATO in inducing differentiation. ATRA can bind to RA nuclear receptor. By binding to PML/RARα, all-trans retinoic acid promotes the dissociation of PML/RARα complex and activates the expression of differentiation-related genes. The re-expression of these genes leads to the differentiation and maturation of leukemia cells. At the same time, all-trans retinoic acid also reduces the malignancy of leukemia cells by inhibiting their proliferation. Through its unique mechanism, it

can not only induce the differentiation of leukemia cells and restore normal hematopoiesis, but also inhibit the proliferation of abnormal cells and reduce the malignant degree of leukemia cells. However, due to its insufficient targeting, it often leads to the similar inhibition of normal hematopoietic cells, often accompanied by anemia and hemorrhage, a problem that is prone to occur in patients with APL.

The combination of ATRA and ATO represents a promising therapeutic prospect for future clinical research. In experiments at APL clinical centers in Germany and Italy, 263 patients with newly diagnosed, low-or moderate-risk APL were randomized to either ATRA-ATO or ATRA-CHT. The results of this study showed that the ATRA-ATO regimen was more effective against leukemia, and other prognostic indicators such as event-free survival, overall survival, and disease-free survival were significantly better than the initial results. In both groups, complete remission was achieved in 100% and 97% of patients (Shigeno K, Naito K, Sahara N, Kobayashi M, Nakamura S, Fujisawa S, et al, 2005). At the median follow-up of 40.6 months, the event-free survival, cumulative recurrence rate, and overall survival improved significantly in the ATRA-ATO group, at 97.3% /80%, 1.9% /13.9%, and 99.2% /92.6%, respectively. Quality of life analysis showed that after induction treatment, the fatigue strength of ATRA-ATO group was significantly lower than that of the control group. These data indicate that the benefits of ATRA-ATO increase over time. In the treatment of low or moderate risk APL, the use of regimens including ATO not only reduces the risk of death and blood toxicity, but also results in a higher and more durable anti-leukemia effect without additional fatal events and relapses. Therefore, in this time of increasing patient base, the combination therapy with ATO and ATRA as well as other drugs can provide reliable guarantee for reducing the mortality and recurrence rate of patients.

5. Toxicity and Adverse Reactions of Arsenic Trioxide

Arsenic has been a known as a highly toxic drug since ancient times, and it was first recorded in Kaibao Materia Medica of the Song Dynasty in China (Huang Yanan, 2014). ATO is its main component and a carcinogen. As for its toxicity, there are different manifestations of acute toxicity and chronic toxicity. After arsenic enters the body, it can combine with protein and amino acids in the blood and distribute to various organs throughout the body along with the blood flow. The toxic effect of arsenic is combined with the enzyme in the body, the sulfhydryl group and hydroxyl group in the molecular structure of protein to inactivate the enzyme, thereby interfering with the normal metabolism of cells, affecting the process of respiration and oxidation, causing cell lesions and inhibiting cell division and proliferation (ZHANG Jing-yi, SUN Gui-bo, WANG Min & SUN Xiao-bo, 2016). In addition, arsenic can directly damage the arteriole and capillary wall, and act on the vasoconstriction center, resulting in increased vascular permeability, decreased blood volume, and aggravated the damage of flatulence. The main clinical manifestations of arsenic poisoning are nausea, vomiting, abdominal pain, diarrhea, watery stool, causing dehydration and circulation failure (SUN Jiafu, SUN Xiao, SUN Guibo, SUN Xiaobo, NAN Fengwei, LUO Yun, GAO Ye & WANG Shan, 2020). The central nervous system can be agitated, delirium, limb muscle spasm, confusion, and even coma, finally died of respiratory center paralysis. Acute arsenism can also be complicated by acute renal failure, toxic hepatitis and toxic myocarditis. Chronic arsenic poisoning is mainly manifested as neurasthenia.

The main toxicities of ATO therapy in the remission induction phase were APL differentiation syndrome (fever, body weight gain, polyserositis, respiratory distress and lung infiltration, and in severe cases, respiratory failure, renal failure, and pulmonary hemorrhage) (Zheng JL & Gong XZ, 2018). Approximately one third of patients develop this complication. The primary cause of induction response failure was APL differentiation syndrome. Other toxicities included hepatotoxicity, nephrotoxicity, neurotoxicity, metabolic disorders (hyperglycemia, hypomagnesemia, and hypokalemia), fluid retention, skin discoloration, xeroderma, and conjunctivitis (Chai Xinmin, Zhao Xiaoyan, Lu Yanjie, et al, 2009). Typically, none of these complications jeopardize successful disease control by ATO. These complications are very rare in the consolidation phase, so the complications may be due to the toxic effects of the drugs and the toxic products of leukemia cells. At the same time, other studies have shown that another

major complication is QTc prolongation, which can lead to heart-related sudden death. Although the possibility of arrhythmia in clinical studies is not high, it is essential to maintain the detection of QTc during treatment and to maintain the potassium and magnesium intake to ensure patient safety.

6. Potential Application of Arsenic Trioxide Outside APL

Due to its unique cytotoxic effect and mechanism of inducing apoptosis and differentiation, ATO also has good effects on other cancers and autoimmune diseases. For example, in the treatment of primary liver cancer, the results of cell culture experiments and in vivo animal experiments have shown (Hu, 2014) that ATO has a significant effect of inhibiting the growth, proliferation and inducing apoptosis of liver cancer cells. The molecular mechanism of inducing apoptosis is achieved by down-regulating bcl-2, increasing the expression of bax, and changing the ratio between the two. A certain concentration of ATO affects cell cycle kinetics, blocks hepatoma cell SMMC-7721 in G2-M phase and S phase, and prevents cell mitosis, thereby prolonging cell cycle time and inhibiting hepatoma cell proliferation. The results showed that the effective rate of ATO in the treatment of advanced liver cancer was 16.0%, which significantly improved the quality of life and prolonged the survival time, with mild toxic and side effects. Moreover, ATO had significant analgesic effect on some patients with liver pain, thus providing a new idea for the treatment of liver cancer.

In addition, the investment of ATO in the treatment of bronchial asthma is also worth exploring. Bronchial asthma is an allergic inflammatory disease characterized by high responsiveness of the airway. The formation of this feature is mainly due to the accumulation and activation of eosinophils in the airway mucosa and the proliferation of white blood cells and T cells. However, according to the experimental results of ATO administered to an asthmatic mouse model by Liang Biao et al. (2004), ATO significantly reduces the number of eosinophils and T cells in the mouse, and the total number of white cells also shows a downward trend, and the decreasing amplitude increases with the dose. This experiment confirmed that ATO could significantly down-regulate the gene expression of Bcl-2 in mice, leading to the apoptosis of T cells. At the same time, studies have pointed out (Nakamuro K, 1981) that ATO directly affected the mitosis of lymphocytes and inhibited cell proliferation through cytotoxic effect at higher concentrations, thereby reducing the number of T cells and eosinophils and achieving the effect of relieving asthma.

Moreover, ATO has wide-ranging effectiveness in the treatment of other cancers, for example, ATO can be used in combination with doxorubicin (ADM) for the treatment of breast cancer. Although ADM has a significant effect on breast cancer, it is prone to drug resistance (WANGX N, WANG K Y, ZHANGX, et al, 2018). ATO can partially reverse the resistance of drug-resistant MCF-7/ADM to ADM by increasing the concentration of ADM in MCF-7/ADM and regulating glutathione S-transferases (GSTs) activity. Moreover, if ATO is used in combination with low-dose salinomycin, it can inhibit the proliferation and promote the apoptosis of breast cancer cell MCF-7 (ZHOU M S, WANG S S, WANGY, et al, 2018).

According to the induction mechanism of ATO on apoptosis and the unique cytotoxic effect, breast cancer, lung cancer, multiple myeloma, systemic lupus erythematosus, nasopharyngeal carcinoma, rheumatoid arthritis and other diseases similar to the pathogenesis and treatment path of the above diseases have made gratifying progress after they were put into treatment. Therefore, the application of ATO should not only focus on the cure of APL, but also show excellent application prospect in addition to APL.

7. Future Research Direction of Arsenic Trioxide

Despite the established track record of ATO in complete response and population coverage, the efficacy and side effects of ATO are still poorly balanced, potentially destabilizing therapeutic outcomes. In order to achieve the purpose of reducing toxic and side effects and improving the treatment effect, according to the research there are several ways as follows. First, ATO was administered through bone marrow targeted nanoparticles. The research group from China conducted the pharmacokinetic study of arsenic trioxide bone marrow targeted nanoparticles through mouse model (Wang Xueying, et al, 2008). The results showed that after intravenous injection, the samples could quickly enter the

blood system with good bioavailability. Meanwhile, the half-life of this sample was long, and the retention time was significantly increased, indicating that this sample had good stability in vivo. The curve of blood concentration versus time showed that the nanoparticles could persistently release arsenic trioxide for a certain period of time, so as to better exert its therapeutic effect. The study has proved that arsenic trioxide bone marrow targeted nanoparticles have good bone marrow targeting and pharmaceutical activity, and have good pharmacokinetic properties, reduce the toxic and side effects, improve the safety.

Second, protein microspheres were also a possible choice for sustained and controlled release administration of ATO. Zhou et al. (2005) connected the monoclonal antibody BDI-1 with strong specificity for bladder tumors to protein microspheres to achieve targeted therapy for ATO. They prepared the monoclonal antibody BDI-1-oriented ATO immune protein microspheres by the method of protein crosslinking curing and N- hydroxysuccinic imino -3-(2- arsenic disulfide)-propanoate (SP-DP) crosslinking. The covalent attachment and activity of ATO immune microspheres were characterized by reduction electrophoresis, light and electron microscopy. Apoptosis of tumor cells was detected by acridine orange staining. The results showed that the prepared immune protein microspheres were connected by covalent bonds and could specifically bind to bladder tumor cell BIU-87 to play a role in inducing apoptosis. This provided the basis for reducing the toxic effect of ATO and achieving its specific killing on bladder tumor cells. However, since the relevant data on the animal experiments or clinical studies on the introduction of immune microspheres are still small, they still need the attention of more scholars.

Finally, liposomes also show good potential in reducing the toxicity of ATO and improving the therapeutic effect. Zhang et al. (2007) used lecithin, cholesterol and vitamin E as raw materials to prepare ATO liposomes by ultrasonic film dispersion method. In this experiment, the effect of the prepared ATO liposome on mouse glioma was also studied, and it was found that the liposome could induce apoptosis of mouse glioma cells more significantly than ATO and prolong the survival time of tumor-bearing mice. Glioma is the most common malignant tumor in the central nervous system, and it has become an urgent task to explore new effective treatments for glioma. However, ATO has a low permeability to the blood-brain barrier and is difficult to treat intracranial tumors, which has become an obstacle for clinical application research. Therefore, the liposome drug delivery system provides a new way for the in vivo application research of arsenic trioxide. In summary, the new preparations are undoubtedly an effective and convenient way to improve the treatment protocol of ATO. Due to the sustained and controlled release characteristics of these preparations, the survival rate of patients is effectively improved, and the toxic and side effects are reduced, which will be the main development direction in the future.

8. Conclusion

Given the demonstrated efficacy of ATO in treating APL and the growing interest in repurposing traditional drugs, further investigation into ATO's therapeutic mechanisms, potential combination therapies, and pharmacokinetic properties both in vitro and in vivo is essential. This review provides a detailed analysis of the latest research on ATO, including its toxicity profile and future application prospects. Due to its unique mechanisms of inducing apoptosis, promoting differentiation, exerting cytotoxic effects, and selectively targeting certain cancer cells, it is anticipated that future studies will enhance our understanding of its mechanisms in combination therapies and expand its clinical use. Additionally, increasing efforts will likely focus on mitigating toxicity, thus broadening its scope in clinical practice.

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