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From Mechanism to Clinical Application: Exploration of Arsenic Trioxide (ATO) in the Treatment of Acute Promyelocytic Leukemia and in Other Types of Leukemia

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Abstract. Acute promyelocytic leukemia (APL) can form characteristic oncogenic fusion proteins, and traditional chemotherapy can cause serious adverse reactions. Clinically, targeted therapies with better safety have been explored. Existing research has confirmed the therapeutic effect of Arsenic trioxide (ATO) on this type of leukemia, but there is still a lack of systematic summary on whether it can be used for other types of leukemia. This article summarizes the development history, mechanism of action, and clinical use of ATO, compares the therapeutic effects of drugs in leukemia with and without PML-RAR α targets, and confirms that specific targets directly determine whether drugs can exert targeted efficacy. The content of this review can provide a reference for clinical arsenic agent selection and subsequent mechanism research. At present, the academic community still lacks complete long-term safety data for the long-term administration of arsenic drugs. Subsequent research can further optimize the administration method, try low-toxicity combination therapy, and further explore the potential application of arsenic drugs in tumor treatment.

Keywords: Arsenic trioxide (ATO), Leukemia, PML-RARα, Apoptosis, Targeted therapy

1. Introduction

Leukemia is a malignant hematological disorder characterized by the abnormal proliferation of hematopoietic stem cells [1]. Among its various subtypes, acute promyelocytic leukemia (APL) was considered one of the most aggressive and fatal types because of its quick progression and high mortality rate. Chemotherapy has been the mainstay of treatment, but most chemotherapy treatment regimens have significant side effects, especially the damage to normal cells due to the non-specific cytotoxicity. Consequently, the development of more targeted and safer treatment that have emerged as a key area of medical research.

Arsenic trioxide (ATO), commonly known as "arsenic" or "white arsenic," was long regarded as a highly toxic substance. However, modern medical research has demonstrated that, at specific doses and under defined conditions, As_2O_3 shows remarkable therapeutic efficacy in APL, and it has subsequently evolved into one of the first-line treatments for this disease [2]. This phenomenon of

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"using a toxic agent to achieve therapeutic benefit" has attracted wide attention and propelled in-depth investigation into its mechanism of action.

Previous research has shown that ATO can bind to the APL-specific PML-RARα (promyelocytic leukemia–retinoic acid receptor alpha) fusion protein at the molecular level, degrades it and in this way regulates cellular differentiation and apoptosis, thereby blocking the proliferation of tumor cells through the regulation of cellular differentiation and apoptosis. To date, research on ATO for the treatment of APL has evolved from the conventional "ATRA (all-trans retinoic acid) + chemotherapy" paradigm into a new standard centered on a chemotherapy-free "ATRA + ATO" regimen. The final long-term follow-up of the Italian-German phase III randomized APL0406 trial confirmed that in low-/intermediate-risk APL, the ATRA+ATO regimen achieved a 72-month event-free survival (EFS) rate of 96.6%, significantly superior to the 77.4% observed in the ATRA+chemotherapy group ($P<0.0001$), with an overall survival (OS) rate of 98.3% versus 89.8% ($P=0.004$) [3]. Moreover, hematologic toxicity was significantly reduced, establishing ATO's cornerstone position in the first-line treatment of APL.

In terms of optimizing treatment convenience, the primary trend in drug development is the use of oral arsenic formulations. The Chinese multicenter phase III randomized controlled APL07 trial enrolled 243 newly diagnosed APL patients to compare the efficacy of oral arsenic (Compound Huangdai Tablets) with intravenous ATO, both combined with ATRA. The results demonstrated no statistically significant differences between the two groups in complete remission (CR) rate (99.1% vs. 97.2%), disease-free survival (DFS) rate (98.9% vs. 97.6%), or overall survival (OS) rate (99.1% vs. 96.6%) [4]. Updated data from a median follow-up of 61 months further confirmed that the 7-year EFS and OS rates in the RIF group were 93.7% and 95.4%, respectively, comparable to those in the ATO group (89.4% and 90.9%) [5]. These findings validate the convenience of oral arsenic administration, positioning it as an ideal first-line treatment option for APL. Therefore, this paper focuses on systematically analyzing the molecular mechanisms of ATO in leukemia treatment, evaluating its clinical efficacy and limitations, with the aim of deepening the understanding of targeted therapy strategies and providing references for future research.

2. Molecular basis of APL and the therapeutic principles of ATO

2.1. Molecular basis of APL

2.1.1. Chromosome level

APL pathogenesis is driven by a reciprocal translocation between two non-homologous chromosomes. Specifically, the PML gene, originally located on chromosome 15, breaks and fuses to chromosome 17, while the RARα gene, originally on chromosome 17, breaks and translocates to chromosome 15. This genetic rearrangement results in the formation of the PML-RARα fusion gene, which is transcribed and translated into the PML-RARα fusion protein [6]. This oncogenic protein exerts a dominant-negative effect that suppresses granulocytic differentiation genes, leading to a blockade in promyelocyte maturation. Consequently, massive accumulation of abnormal promyelocytes occurs, ultimately culminating in APL leukemia. Under physiological conditions, the PML and RARα genes function independently without forming a fusion protein, thereby ensuring normal hematopoietic differentiation.

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2.1.2. Protein level

The normal PML protein, on the other hand, can dimerize and polymerize through its RBCC domain to form 15-20 nuclear bodies (PODs or PML-NB) in the nucleus. These structures act as regulatory hubs regulating transcription, apoptosis and DNA damage response. The fusion protein, however, upon expression, the PML portion binds to wild-type PML through the RBCC domain, resulting in the formation of hetero-oligomer. This causes disruption of the integrity of PODs, causing hundreds of small granules to be scattered around the nucleoplasm. The remaining wild-type PML is then relocated. These RBCC-mediated heterodimers further disrupt the correct assembly of POD, and ultimately abrogate the physiological tumor-suppressive functions of PML such as inhibition of proliferation and induction of apoptosis, which provides a survival advantage to leukemic cells [7]. However, the fusion protein PML-RARα forms heterodimers with retinoid X receptor (RXR) and is able to bind to retinoic acid response elements (RAREs), and to displace the wild-type RARα from these elements. The fusion protein becomes a dominant negative protein and is able to outcompete the wild-type protein. In addition to binding to RAREs, PML-RARα also brings histone deacetylases (HDACs) to deacetylate histone H3. This deacetylation makes chromatin less accessible and makes it more difficult for RNA polymerase to start transcription of genes [8]. Deacetylated, the HDAC complex can recruit methyltransferases to the catalytic addition of three methyl groups to histone H3 at lysine 9 (H3K9me3), for example SUV39H1. This "trimethylation of H3K9" signal is repressive, inhibiting binding of other transcription activators. Lastly, the PML-RARα complex also brings DNA methyltransferases (DNMT1/3) which introduce methylation to CpG islands in the promoters of genes (DNA methylation). This directly blocks the binding of transcription factors and importantly this repressive epigenetic state is mitotically inherited by daughter cells [9]. Thus, the chromatin region switches from an active euchromatin state to a tightly compacted heterochromatin structure that is not capable of transcription.

2.1.3. Cellular level

The epigenetic silencing caused by the fusion of the PML protein with the RARα is a direct consequence of the inability to induce the program of granulocytic differentiation. In addition to its role in regulating differentiation-associated genes, RARα regulates genes that control the cell cycle, while the PML-RARα fusion protein impairs the tumor-suppressive properties of PML. This provides the cells with a growth advantage that causes promyelocytes to multiply without limit and to maintain their presence. As a result, some critical genes necessary for cell maturation are transcriptionally suppressed and the cells are unable to detect any differentiation signals and remain at the promyelocytic stage. Whereas normal hematopoietic cells proliferate and mature in a well-coordinated fashion, these leukemic cells allow for unrestricted proliferation but no maturation [10].

2.2. Mechanisms of action of ATO

2.2.1. Induction of PML-RARα degradation

Promotion of SUMOylation is the first step in degradation by ATO. The PML protein possesses a unique structural motif, the B2 domain that contains certain cysteine residues which bind ATO. Once inside the cell, ATO directly binds to these cysteine residues in the B2 domain of the PML moiety of the fusion protein PML-RARα, which sets off a chain of enzymatic reactions [11]. The intracellular SUMO E3 ligase, called Protein Inhibitor of Activated STAT (PIAS), is recruited to promote the

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SUMOylation (conjugation to lysine residues) of the PML moiety. This SUMOylation is an important degradation signal that is required for the subsequent clearance of the protein. Then, the ubiquitin E3 ligase RNF4 (RING finger protein 4) binds to the SUMOylated PML protein and adds polyubiquitin to PML. The polyubiquitinated PML-RARα is subsequently targeted to the 26S proteasome for proteolysis and degradation of the fusion protein. Importantly, ATO selectively degrades the fusion protein, but not the wild-type PML and RARα proteins. Thus, free PML can reconstruct 15–20 nuclear bodies (PODs) and regain its tumor suppressive and pro-apoptotic properties. Moreover, upon removal of the RARE sites, the normal gene transcription can be initiated by free wild-type RARα [12].

2.2.2. Induction of apoptosis

In addition to the selective degradation of the PML-RARα fusion protein, ATO also directly induces apoptosis in leukemic cells. ATO is an arsenical agent that is taken up by target cells and disrupts the mitochondrial electron transport chain (ETC), causing a depletion of intracellular glutathione (GSH), an important antioxidant, and resulting in high levels of reactive oxygen species (ROS). The antioxidant defense system is intrinsically compromised in APL cells because the absence of wild type PML as a result of PML-RARα-mediated sequestration and disruption of PML nuclear bodies results in a marked impairment of antioxidant defense system in these cells. Hence, increased ROS levels lead to a loss of intracellular redox balance. Upon redox imbalance, ROS directly damage the inner mitochondrial membrane leading to loss of $\Delta\Psi m$. Then, cytochrome c (Cyt c) is exported from the mitochondrial intermembrane space and is translocated to the cytosol where it interacts with the apoptotic protease activating factor-1 (Apaf-1) to form the apoptosome. The apoptosome triggers the activation of caspase-9 which is the main initiator caspase and triggers the intrinsic pathway of apoptosis. Once activated, caspase-9 proteolytically activates the executioner caspases, caspase-3 and caspase-7, which then cleave a large number of intracellular substrates leading to the apoptosis of malignant promyelocytes [13].

3. Clinical application results and analysis of ATO

3.1. Clinical effect

In 2018, a control study included 82 leukemia patients for grouping intervention. The complete remission rate of the control group treated with ATRA alone was only 63.41%, while the complete remission rate of the observation group treated with ATO combined therapy could reach 85.37% [14]. Complete remission means that after treatment, the patient's clinical signs and symptoms disappear completely, such as low fever, bone and joint pain, and megakaryocytes and red blood cells return to normal levels. The number of unresponsive cases in the observation group was significantly less. ATO and ATRA can work together to induce the death of abnormal promyelocytes in different ways. Complete and partial remission of the disease can reduce bleeding symptoms, early death, and other high-risk risks. The improvement of remission level can directly improve the long-term survival status of patients, and the ATO combined scheme has significantly improved the survival rate of patients.

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3.2. Safety analysis

Conventional chemotherapy, as the traditional treatment of leukemia, has a prominent killing effect on tumor cells, but the broad-spectrum cytotoxicity of drugs will cause multiple organ damage, and the overall safety of drug use is low. ATO therapy is more targeted, which can specifically combine with leukemia tumors and accurately act on pathological cells. Although ATO itself has primary toxicity, the toxicity of this treatment scheme is less than that of chemotherapy. ATO is a protoplasmic toxin; if the dosage of ATO is too large, it may lead to gastrointestinal symptoms such as abdominal distension, nausea and vomiting, skin lesions such as rash, pigmentation, skin ulcer, and mucosal lesions such as dry throat and oral ulcer. When the situation is serious, it may even lead to death. Therefore, medical staff need to grasp the dosage of ATO [15].

4. Clinical effect and risk analysis of non-APL leukemia

4.1. ATO efficacy in various types of leukemia

4.1.1. Non-APL acute myeloid leukemia (non-APL-AML)

There is no PML-RARα fusion protein target in this kind of leukemia; ATO can not degrade the carcinogenic kinesin and can only induce leukemia cell apoptosis by increasing the level of ROS and activating the caspase-dependent pathway. This mode of action lacks targeting, has weak carcinogenic intensity, limited killing efficiency, and can not completely eliminate leukemia stem cells, so it can not achieve complete remission of the disease alone, and can only be used as an adjuvant in the clinic.

4.1.2. Chronic myeloid leukemia (CML)

The core driving mechanism of these diseases is the continuous activation of tyrosine kinase by the BCR-ABL fusion gene, which promotes the malignant proliferation of leukocytes and inhibits the normal hematopoiesis of bone marrow. At present, the first-line treatment drugs such as imatinib can precisely inhibit the activity of this kinase. ATO can neither bind to the BCR-ABL fusion protein nor block the downstream carcinogenic signaling pathway, so the inhibitory effect of ATO on CML is far weaker than that of standardized targeted drugs. However, as an adjuvant, the combination therapy of ATO and BTZ can induce apoptosis in many leukemia cell lines. As_2O_3 and BTZ interact synergistically to enhance the apoptosis of imatinib-sensitive cells. BTZ, whose full name is bortezomib, is a proteasome inhibitor widely used in the clinic, mainly for the treatment of hematological malignancies.

4.1.3. Acute lymphoblastic leukemia (ALL)

The pathogenesis of the disease is mostly related to lymphocyte dysplasia and gene mutation accumulation, and there is no molecular target suitable for ATO. At present, there are few studies on the application of ATO in acute lymphoblastic leukemia, but studies have found that within a certain concentration range, Atorvastatin Combined with ATO significantly enhanced the apoptosis of ALL cells and significantly increased the anti-proliferation effect. Low-dose arsenic can be combined with basic treatment to help reduce the tumor load and improve the short-term condition of patients [16].

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In general, whether tumor cells have specific targeted fusion proteins is the core premise to determine the therapeutic effect of ATO.

4.2. Comparison of treatment schemes: chemotherapy, targeted new drugs, ATO adjuvant therapy

Traditional chemotherapy is the basic means of leukemia treatment. It can effectively inhibit the proliferation of malignant tumor cells in bone marrow by killing rapidly dividing and proliferating cells with a broad spectrum, which is suitable for all leukemia subtypes. However, chemotherapy lacks tumor specificity, which can kill cancer cells and damage a large number of normal cells at the same time, and the overall treatment risk is high.

Subtype-specific targeted drugs are the core direction of precise treatment of leukemia. For example, imatinib and other drugs can accurately bind to various leukemia characteristic fusion proteins or mutant kinases to accurately block carcinogenic signaling pathways. These drugs have strong pertinence, little damage to normal cells and stable long-term efficacy, and have become the preferred treatment for CML, partial mutant AML and other subtypes.

ATO does not have the ability of broad-spectrum targeted anti-tumor, and cannot adapt to the core pathogenesis of most leukemia subtypes. ATO has a weak anti-tumor effect, can not cure the disease alone, and belongs to heavy metal drugs, which have toxic effects after long-term use. Therefore, it can only be used as a supplementary adjuvant therapy in the overall treatment system, and cannot replace the mainstream first-line drugs.

4.3. Difference in toxicity risk of arsenic used in non-APL leukemia

In the treatment of leukemia with specific targets, a short course of treatment and standardized dose can be used to achieve efficient treatment. The cumulative dose of arsenic is controllable and the toxicity is mostly mild. However, in the treatment of all kinds of non-APL leukemia, due to the weak efficacy of the arsenical agent itself, it is often necessary to increase the dosage, prolong the treatment cycle, and repeat the course of treatment many times to strive for a weak tumor inhibition effect.

Long-term, high-dose arsenic application will significantly increase the risk of systemic toxicity. Prolonged QT interval and persistent abnormal liver function were the most common. Long-term accumulation of arsenic in the human body can cause chronic irreversible organ damage. When arsenic is used for the treatment of non-APL leukemia patients, the treatment benefit is limited, but the toxicity risk is significant, and the benefit-risk ratio is low.

5. Conclusion

This study reviewed the relevant content of ATO for the treatment of APL, sorted out the development history, molecular mechanism of action, and actual clinical effects of the drug, and compared and discussed its limitations in other subtypes of leukemia, confirming that specific targets are the core condition for determining drug efficacy. In response to the question raised at the beginning, this article clarifies that ATO cannot combat various types of leukemia in a broad spectrum and can only exert targeted effects in the presence of PML-RARα fusion protein. This conclusion can also provide ideas for clinical drug judgment and subsequent mechanism research. Due to the limited research format of the review, this article cannot include unpublished clinical trial results, and the exploration of long-term side effects caused by drug use is not in-depth enough.

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Subsequent research can attempt to optimize the administration method, explore safer combination therapy regimens, reduce organ damage caused by arsenic agents, and continue to explore the potential applications of such drugs in more tumors.

Author contribution

All the authors contributed equally and their names were listed in alphabetical order.

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