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Review

Clinical Implementation of Arsenic Trioxide

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ABSTRACT

Introduction of arsenic trioxide (ATO, As2O3) to the treatment of acute promyelocytic leukemia in the 1970s enlightened an effective treatment approach for the disease. Decades later, knowledge on this agent’s further functions has rapidly advanced so that it has entered common use in hematology and oncology. In addition, As2O3 reportedly induces DNA and chromosomal damage, inhibits DNA repair, and alters DNA methylation in mammalian cells. The compound is becoming increasingly reasonable as a treatment modality to rectify genetic blood disorders and other cancer types. Nevertheless, limitations of As2O3 typically emerged from drug resistance, adverse effects and secondary tumors, which may result in a myriad of outcomes. Though prolonged exposure to As2O3 ensues poisons and genome alternations that do not permanently change the DNA sequence, other synergistic alterations should be considered as replacement. In this review, we recollect the discovery and clinical implementation of As2O3, describe its advantages and shortcomings for leukemia and solid cancer treatment, and consider future prospects for engendering useful impacts.

Key words

acute promyelocytic leukemia; advantages; arsenic trioxide; shortcomings; side effects; therapeutics

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1. Introduction

Arsenic trioxide (ATO, As2O3) was first found to be effective in the treatment of acute promyelocytic leukemia (APL) at the First Affiliated Hospital of Harbin Medical University (FAHIMU) in China in the 1970s (Zhang et al, 1984). Afterwards it has been studied as a potent choice for APL patients worldwide, a safe and effective anti-APL therapy of both long- and short-term (Zhou et al, 2010b; Wang et al, 2014). Current opinions regard it as the most effective single reagent for APL treatment (Daver et al, 2015; Coutre et al, 2014; Seftel et al, 2014). Following the discovery of immense potential cytotoxicity of ATO in solid malignant tumors including the breast cancer, the lung cancer, neurogliomas, etc., we are trying to learn more functions of this traditional Chinese medicine (Cheng et al, 2016; Jiang et al, 2004; Chow et al, 2004).

In spite of being poisons, arsenic metabolites have been proved to increase cellular reactive oxygen species (ROS) as a potential inducer of genomic instability through DNA damage,
DNA repair or telomere dysfunction (Kryeziu et al, 2016; Woo et al, 2002). The DNA damage induced by these modalities can silence tumor suppressors such as pro-apoptotic genes or activate proto-oncogenes that in turn lead to genomic instability and cellular transformation, and apoptosis is eventually induced. The cell apoptosis in response to ATO can decrease mitochondrial membrane potential and increase caspase-3 activation and DNA fragmentation. However, ATO as a double-edged sword can strongly damage DNA sequences, leading to a myriad of adverse effects that include cancers of the skin, the lung, the liver, and the bladder (Bhattacharjee et al, 2013; Andrew et al, 2009; Burgdorf and Hoenig, 2014).

ATO (acute myelocytic leukemia-M3) is characterized with cytogenetic abnormality of t (15;17) translocation and PML-RARα fusion oncoprotein. ATO at a low dose can induce cell differentiation by targeting the PML-RARα protein, whereas at a high dose induced apoptosis. Here we reviewed the anticancer history of ATO, described its advantages and shortcomings for leukemia and solid cancer treatment, and considered future prospects for engendering useful impacts.

2. Milestones of development of ATO as a remedy for APL

2.1 Discovery of therapeutic efficacy of ATO for leukemia

ATO, called Pi Shuang in TCM with serious toxicity, has a medicinal history of over 2400 years in China. It is used to treat malignancies based on the “like cures like” principle in TCM. However, not until 1970s has ATO been purposely used to treat leukemia patients. The person who first discovered the effectiveness of ATO in fighting leukemia is Ting-dong Zhang, a Chinese physician and scientist at FAHHMU. His group carried out clinical observation at FAHHMU. The results were of particular significance in clinic, because the first paper on ATO treatment for leukemia patients in which the chemical composition and application of ATO were described in detail (Zhang et al, 1973).

2.2 Validation of ATO for treatment of APL in small-scale clinical trials

After this discovery, Zhang spent a few years on ATO treatment for acute myelocytic leukemia (AML). In 1979, Zhang et al reported that ATO was highly effective in “promyelocytic type” with the total remission rate of 70% in 55 AML patients administrated with ATO (Zhang, 1979). In 1984, Zhang reported that 22 AML patients including 15 APL obtained CR after ATO treatment at FAHHMU (Zhang, 1984). Those findings were paid great attention by both physicians and researchers in China.

2.3 Introduction of ATO treatment for APL to Western medicine

Clinical applications and laboratory experiments of more than 20 years showed the effectiveness of ATO in the treatment of leukemia in China, however, not until 1996 has ATO treatment for APL been known worldwide. During 1996 to 1997, Zhu Chen of Shanghai Rui Jin Hospital reported the molecular mechanism of ATO treatment for APL. So researchers can clearly understand the way ATO works.

In 1996, Chen et al demonstrated that ATO induces NB4 cell apoptosis with down regulation of Bcl-2 expression and modulation of PML-RARα protein, which was published in Blood (Chen et al, 1996). These experiments were reproduced in cultured primary APL cells, all-trans retinoic acid (ATRA)-susceptible (NB4 cells), and ATRA-resistant (MR2 subclone) APL cell lines (Chen et al, 1997).

In 1997, Wang and Chen investigated the clinical efficacy and pharmacokinetics of ATO in relapsed APL patients. The paper entitled “Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients” published in Blood, is the first English paper on the extraordinary therapeutic efficacy of ATO in treating APL (Shen et al, 1997). This report showed that 14 of 15 relapsed APL patients, including two at the second and two at the third relapse, achieved CR after ATO treatment. The results are of particular significance in clinic, since relapsed APL patients have relatively poor prognosis, leading ATO treatment for APL famous to the world. Due to its anti-leukemia bioactivity, the drug Trisenox PolaRx was produced by Biopharmaceuticals that was approved by the US FDA in the year of 2000 and subsequently marketed and sold by Cephalon. Ever since then, ATO has been worldwide used for the treatment of APL that is unresponsive to ATRA, and the joint therapy of ATO and ATRA has also been approved by FDA for the treatment of certain leukemias. After that ATO treatment for APL was accepted by the Western world.

2.4 Control of side effects of ATO in treatment of APL

Due to the toxicity, ATO risk was gradually unraveled in its clinical applications. The side-effects of ATO include hematologic toxicity, cardiac toxicity, neurologic toxicity, and hepatic toxicity. They were described in detail in Part 4. It is urgent to control side effects of ATO in order to ensure the clinical safety and therapeutic efficacy. So we developed a new ATO-delivering method in 2004, namely “continuously slow ATO intravenous infusion”, a successful avoidance from toxicities of ATO (Zhou et al, 2005; 2004) described in detail in Part 5.

3. Advantages of ATO in treatment of APL

3.1 Clinical studies in relapsed APL

ATO started to be used in the treatment of relapsed APL
patients in 1998. A study in 12 relapsed APL patients who had received one or more courses of chemotherapy (ATRA and anthracycline) revealed that 11 of 12 patients achieved CR after ATO treatment, and eight CR patients even reached molecular remission which was indicated by the absence of PML-RARα fusion transcripts (Soignet et al, 1998). In 2001, Soignet et al also reported on the considerable therapeutic effects of ATO in treating relapsed APL (Soignet et al, 2001).

3.2 Clinical studies in primary APL

After its application in relapsed APL patients, ATO started to be used in primary APL patients.

Shen et al (2004) conducted a clinical trial: 61 primary APL patients were randomly grouped into ATRA treatment, ATO treatment, and joint treatment of the two drugs. They found that ATO treatment was similar to the others in CR rates, and the joint treatment could bring a lower relapse rate.

A clinical trial by Mathews et al indicated that ATO treatment for primary APL achieved a CR rate of 86.1% (Mathews et al, 2006b). Another report showed that the ATRA and ATO joint treatment achieved a overall response rate of 92% and three of 75 responders experienced relapse at 39, 52, and 53 weeks, respectively. The authors concluded that the joint therapy was superior to primary APL patients (Ravandi et al, 2009). Powell et al reported that event-free survival was significantly better for patients who received ATO consolidation (Powell et al, 2010). Since CR was achieved in all 77 patients in the ATRA + ATO group yet 75 of 79 patients in the ATRA-chemotherapy group in clinical trials, Lo-Coco et al concluded that ATRA plus ATO therapy was at least not inferior and might be superior to ATRA-chemotherapy in the treatment of patients with low-to-intermediate-risk APL (Lo-Coco et al, 2013). According to the clinical trial including 105 primary APL patients who were treated with a standard induction and consolidation regimen including ATO, Coutre et al suggested that the maintenance therapy might not be needed if patients with low or intermediate risk APL were treated with an intensive post-remission regimen including ATO (Coutre et al, 2014). Efficace et al provided the health-related quality-of-life results of ATRA plus ATO therapy and supported it as a preferred first-line treatment in patients with low- or intermediate-risk APL (Efficace et al, 2014). Daver et al reported that in leukocytosis patients ATRA plus ATO plus cytotoxic therapy could achieve 100% CR rate and 100% 3-year overall survival (OS) rate, in contrast to 57% CR rate and 35% 3-year OS rate of non-ATRA/ATO treatment. Therefore, they suggested that ATRA/ATO-based joint therapy was superior to other regimens for treating leukocytosis (Daver et al, 2014).

ATO in reduced-chemotherapy or chemotherapy-free approaches in the first-line treatment has reduced some of the toxicities associated with anthracycline-based approaches (Sefel et al, 2014). Even in the cohort of patients with therapy-related APL (t-APL), ATO plus ATRA for induction resulted in a similar CR rate compared with ATRA plus chemotherapy (89% vs 70%), and ATO and ATRA may be preferable in t-APL patients to avoid any risk of anthracycline-induced toxicities (Dayyani et al, 2011). Having analyzed 1 397 APL patients in the United States between 1975 and 2008, Chen et al concluded that ATO alone or plus ATRA was an excellent option for older patients who often cannot tolerate anthracycline-based therapy (Chen et al, 2012).

ATO is one of the most effective and safe agents for APL (Mathews et al, 2010; Ghavamzadeh et al, 2011). Our studies suggested that it is also suitable to children and senior-patients (Zhang et al, 2013; Zhou et al, 2010a).

4. Side effects of ATO

4.1 Leukocytosis

The leukocyte counts increases in 1–2 weeks after ATO treatment in patients, even a few patients died from it, which is similar to ATRA syndrome including dyspnea, fever, systemic edema, lung infiltration, pleural, and pericardial effusion. And patients with white blood cell (WBC) count below $10 \times 10^9/L$ at relapse had better survival than those with $WBC$ count over $10 \times 10^9/L$ (Niu et al, 1999).

4.2 Cardiac disorder

Cardiac disorders occur in some patients in ATO treatment, including palpitation, chest depress, precordialgia, arrhythmias and corresponding ECG changes especially QT interval prolongation, which are generally reversible. QT interval prolongation is the most common cardiotoxicity of ATO. Soignet et al found that 63% of all 40 ATO-treated APL patients developed QT interval prolongation. Long QT (LQT) syndrome, a risk factor of developing polymorphic ventricular tachycardia, may raise sudden death incidence of ATO-treated patients. However, there are few reports on cardiac deaths related to arrhythmia treated with ATO. Westervelt et al reported on three sudden death cases in ATO (0.1 mg/kg per day)-treated APL patients. By autopsy, only one of these cases was confirmed as asystolic death (Westervelt et al, 2001).

The mechanism of ATO-induced QT interval prolongation is resulted from ATO influence on cardiac ion channels. A study showed that long term exposure to ATO increased calcium currents and reduced cardiac potassium channel-HERG at cell surface (Ficker et al, 2004). ATO is also found to block both IKr and IKs at clinically relevant concentrations (Drolet et al, 2004). In addition, Yang’s group has found that clinical relevant concentration of ATO could also induce H9c2 cells apoptosis via activating caspase-3 pathway which pointed out another possible mechanism of ATO-related cardiac toxicity (Zhao et al, 2008a). Resveratrol can be used as a protective agent against ATO-induced cardiotoxicity: Yang’s group demonstrated that resveratrol can effectively correct ATO-induced QT prolongation, ventricular structural abnormalities, and myocardial oxidative damages (Zhao et al, 2008b).
4.3 Hepatotoxicity

It is documented that ATO induces hepatotoxicity in 33% of APL patients (Unnikrishnan et al, 2001), and even more often in primary APL patients (Sumner et al, 2000). Wang et al reported that the liver plays a critical role in ATO methylation and is an essential target organ of ATO toxicity (Wang et al, 2013), which are explanations for the observed hepatotoxicity of ATO.

It has been demonstrated that ATO-induced hepatotoxicity can be attenuated by hepatoprotective drug or ATO suspending (Hao et al, 2013). In primary APL patients with ATO treatment alone, occurrence of hepatotoxicity in induction, consolidation and maintenance treatment is 65.5%, 10.3%, and 20.7%, respectively. Hepatotoxicity largely presents as higher levels of ALT and AST enzymes in the liver (Mathews et al, 2006a). But this phenomenon of high serum enzymes is transitory and reversible (Wang et al, 2013).

4.4 Hemorrhage

Severe hemorrhage complications account for 70% of early death in ATO-treated APL patients. Nearly 80% of the fatal bleeding is developed in the central nervous system. ATO-related hemorrhage is typically developed within seven days after the initiation of the therapy and coagulation abnormalities can be alleviated rapidly (Soignet et al, 2001). Tissue factor (TF) is considered to play an important role in bleeding complications. The hemorrhage risk is lower in the ATO treatment than in the daunorubicin-based therapy, possibly attributable to the distinct extent of translocation of phosphatidylserine (Zhou et al, 2011; 2010a).

4.5 Other side effects of ATO

Slight edema, weight gain, and skin pigmentation occur in patients after ATO treatment. ATO treatment can also cause some mild level side-effects, including hypokalemia, hyperglycemia, slightly peripheral neuropathy (DPN), neutropenia, thrombocytopenia, gastrointestinal functional disorder, fever, erythra, different degrees of water sodium retention, etc (Lengfelder et al, 2012).

5. New approaches to controlling ATO toxicity

ATO has dual effects on leukemia cells: promoting apoptosis at high concentration (more than 1 μmol/ L) and enhancing partial cellular differentiation at low concentration (0.1–0.5 μmol/ L) (Zhao et al, 2001). For ATO is effective and safe with minimal side-effect in treating APL, it is important to enhance its apoptosis-inducing ability and to avoid its cell differentiation-promoting action. When ATO is infused at a regular speed and routine dosage, it will remain at higher levels only for a few hours in the circulation system. After the circulating concentration is dropped, ATO can enhance cellular differentiation of leukemia cells which directly cause leukocytosis. In 2004, we established “continuously slow ATO intravenous infusion”, a new infusion method that is able to keep ATO at relatively high level in the circulation system for a longer period.

We first applied the method in 48 APL patients. The dosage of ATO was 0.16 mg/kg × body weight (kg) which was diluted in 5% cartose (500 mL). Patients were infused continuously for 18–20 h every day at a speed of 8 drops/min. The pharmacokinetic analysis revealed that the concentration-time curve was stable without a remarkable concentration peak (Zhou et al, 2004). In 2005, we conducted a compare study in 40 APL patients: 20 patients treated with “continuously slow ATO intravenous infusion” and 20 with ordinary administration protocols as control. We found that a constant, high circulating concentration of ATO can be maintained for a long period of time without a remarkable concentration peak in the treatment of continuously slow ATO intravenous infusion, which not only enhanced the apoptosis-inducing effects but also eliminated cell differentiation. This regimen can obtain maximal therapeutic benefit and decrease leukocytosis incidence (Zhou et al, 2005). Compared with the regular method, the “continuously slow ATO intravenous infusion” reduced the incidence of LQT from 25.0% to 8.1% (Zhou et al, 2004). Other side effects of ATO are mild and controllable even in children and elderly APL patients when the single-agent ATO regimen is used (Zhang et al, 2013; Zhou et al, 2010b).

Conflict of interest statement

The authors declare no competing financial interests.

References

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